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Proceedings of the Second European Symposium on Paraquat Poisoning, 27th January 1986, Guy's Hospital, London

EDITORIAL

PAPERS

continued overleaf

SHORT REPORTS

Human Toxicol. (1987), **6**, 3–6

Editorial

The Second European Symposium on Paraquat Poisoning, 27th January 1986, Guy's Hospital, London

It is now over ten years since the first International Symposium on the Clinical Aspects of Paraquat Poisoning was held in Manchester, England.[1] More recently a WHO monograph[2] on paraquat and diquat has reviewed the action, uses, kinetics and clinical effects of these herbicides following both occupational exposure, and accidental and suicidal poisoning. Treatment was not, however, considered in any detail in the WHO Report. Because of this, we felt it appropriate to organise a second symposium, the purpose of which was to obtain a European consensus on the most effective forms of treatment. Considerable interest was shown in the meeting which was attended by 120 delegates from a score of countries, both inside and outside Europe. In addition to nine invited papers, participants were given the opportunity to present free communications and poster demonstrations, and adequate time was allowed for discussion. We have not included a summary of the discussion but have invited speakers to incorporate important comments in their papers, while many of the additional presentations have been included as short reports or abstracts. We believe that the resulting publication represents a comprehensive summary of the epidemiology, clinical features and management of paraquat poisoning.

Clinicians might ask why paraquat is used at all, given its potential toxicity. The uses and usefulness of paraquat were reviewed by Professor G. Sagar.[3] Paraquat has many advantageous properties; it is a relatively non-selective, rain-fast, foliage-applied contact herbicide which is inactivated on contact with most types of soil. Thus, no biologically active residues remain in the soil and planting and sowing may be carried out almost immediately after spraying. It has been estimated that in Europe alone 5×10^6 hectares are sprayed with this herbicide annually and that it is now used in over 130 countries. As yet there is no alternative herbicide which possesses all of paraquat's agrochemical characteristics.

Dr B. Hart reported that paraquat has an excellent safety record if used as directed, and that this has been confirmed by several field studies.[4] Understandably some of the recommended precautions such as the wearing of protective clothing, or a face mask, are not always complied with, especially in tropical conditions. In most cases this does not affect the safety of the product, though the prolonged wearing of clothing contaminated with inadequately diluted paraquat concentrate may result in extensive and severe skin damage, systemic toxicity and, rarely, death. More commonly, minor and reversible injuries to the skin, eyes, nose and nails occur, usually due to poor hygiene or poor agricultural practice.

Dr G. Volans presented data on paraquat poisoning in the U.K. over the twenty-year period since the first fatalities were recorded and examined in detail data for the last six years.[5] In the U.K., fatalities due to accidental poisoning have remained below ten per year and no children have died from paraquat poisoning since 1977. Currently fewer than 50 adults die each year from the deliberate ingestion of paraquat. In contrast there were estimated to be more than 1300 fatalities from this cause in Japan in 1984.[6] Difficulties were found in attempting to compare morbidity and mortality data for paraquat between different countries. The meeting debated this point and consequent to this discussion a paper has been presented to a meeting of the European Association of Poison Control Centres and the World Federation of Clinical Toxicology Centres[7] in order to establish a scheme for standardisation of data collection, using paraquat as a model. A number of countries have since agreed to a pilot scheme with the support of the International Programme on Chemical Safety.

Against this background, the likely effects of preventive measures already introduced were reviewed. Labelling, even if in an appropriate language is unlikely to deter the determined suicide. Moreover, extensive media coverage about the potential toxicity of paraquat may increase the likelihood of suicide. Changes in the formulation of paraquat—for instance the addition of colour, stench and, more particularly, an emetic—have been introduced but have not yet been evaluated satisfactorily. Although several authors have expressed an opinion on the value of the emetic, none have produced adequate evidence to support their conclusions, yet it is disappointing that the addition of an emetic does not appear to have affected mortality significantly.

Two further suggestions were made at the Symposium which might help to prevent serious intoxication, even in attempted suicide, and both provoked considerable interest. The first of these was that there should be a reduction in the concentration of the marketed concentrate from 20% w/v to either 10% w/v[5,8] or 5% w/v.[9] The second suggestion was that paraquat could be reformulated to contain a

natural thickening agent as demonstrated by Professor Naito.[6] When this formulation is mixed with small amounts of water a semi-solid mixture is produced which would make it difficult to ingest large quantities. Unfortunately this formulation is, as yet, only at an early stage of development and further work on its herbicidal performance is necessary. The results of these studies are awaited with interest.

Lastly, in terms of prevention, reduction of availability might be effective in limiting suicidal fatalities. Paraquat has been banned in some countries, for example, West Germany, Sweden and Norway, though not necessarily for toxicological reasons. Such a measure would in time result in the disappearance of paraquat poisoning though it is probable that the determined suicide would substitute equally toxic alternatives. As a result a valuable herbicide would be lost without any diminution in poisoning fatalities. All proposed preventive measures must be considered in toxicological terms initially and then balanced against the agricultural needs of the country concerned.

The clinical features of systemic toxicity were summarised by Dr A Vale.[10] Systemic toxicity more commonly occurs following the ingestion or injection of paraquat. Three degrees of intoxication may be distinguished; mild poisoning (< 20 mg paraquat ion/kg body weight); moderate to severe poisoning (20–40 mg paraquat ion/kg body weight) and acute fulminant poisoning (> 40 mg paraquat ion/kg body weight). Whereas in mild poisoning all patients recover fully and suffer only minimal gastrointestinal symptoms, the majority of patients in the other categories die. In the case of moderate to severe poisoning death is normally delayed two or three weeks and renal failure and pulmonary fibrosis occur. On the other hand, in acute fulminant poisoning multiple organ failure occurs early and death is never delayed for more than a few days.

The most characteristic feature of paraquat poisoning is lung damage. This may be explained by the biochemical mechanisms of toxicity summarised by Dr L. Smith.[11] Paraquat is selectively accumulated in the lung by an energy dependent diamine transport process located in the alveolar epithelial cells and Clara cells of the airways. Paraquat is thought to exert its cellular toxicity by undergoing cyclic oxidation and reduction (redox cycling) to produce free radicals, such as superoxide, and to deplete NADPH. The biochemical consequences of these changes are not clear but may include direct cellular damage by free radicals, e.g. lipid peroxidation, and disruption of essential physiological and biochemical functions, by changes in cellular NADPH and other co-factors and enzymes. Direct evidence of lipid peroxidation *in vivo* is scarce but it is encouraging to see that preliminary studies in man do provide support for this hypothesis.[12] Although the biochemical mechanisms of paraquat toxicity are being resolved, inhibition of redox cycling *in vivo* has not been achieved. Until the biochemical events leading to cell death have been identified more specific treatments cannot be developed.

Professor D. Davies reviewed the pharmacokinetics of paraquat.[13] Data on paraquat absorption in man is sparse but suggests that absorption from the gastrointestinal tract is rapid but incomplete, as in the dog, with peak plasma concentrations occurring at approximately 2 h after ingestion. Thus, procedures to clear paraquat from the gut more than 4–6 h after ingestion are unlikely to be useful and may remove little more than that proportion of the dose which will not be absorbed. It has been proposed that the distribution of paraquat in the body is best described by a three-compartment open model with input to, and elimination from, the central compartment, (the blood). In a computer simulation, the early onset of renal failure produced a five-fold increase in plasma levels of paraquat. Preliminary work in dogs suggests that concentrations of paraquat in the lung may be greatly influenced by the time of onset and degree of renal failure. Thus the biochemical and pharmacokinetic aspects of paraquat poisoning have been identified in some detail. Subsequent speakers repeatedly referred back to this knowledge in discussing treatment but it was clear that in the past many treatments had been proposed without making such reference.

The management of paraquat poisoning was reviewed critically by several contributors. There was agreement that measures to relieve distress and the symptoms caused by ulceration of the oropharynx were of far greater importance than the inappropriate use of heroic measures in patients who, on the basis of quantitative plasma or urine analysis[14,15] were unlikely to survive.[10]

Methods to prevent absorption of paraquat were reviewed by Dr. T. Meredith.[16] Although animal work suggests that activated charcoal[17] and kayexalate[18] reduce the mortality if given within three to four hours of dosing with paraquat, there is no conclusive evidence in man that the use of any method to prevent absorption alters the clinical course of paraquat poisoning.

Dr C. Bismuth[19] and Dr A. Proudfoot[20] assessed the value of haemodialysis and haemoperfusion in increasing the elimination of paraquat following absorption. It was considered unlikely that modification of toxicokinetics by such techniques would improve the treatment of paraquat poisoning as they are usually carried out after a lethal amount of paraquat has been taken up by vital organs. Prolonged haemoperfusion in the small number of patients who are moderately poisoned with paraquat, and who develop early renal failure may be of value, if carried

out within 6–18 h of absorption.[13] It was also considered pertinent to look again at the use of peritoneal dialysis using new osmotic agents. Although this technique is inferior to both haemodialysis and haemoperfusion at removing paraquat, it has the advantage of speed of institution and ease of use.[13]

Appraisal of many of the treatment regimens is limited by the lack of adequate supporting analytical data. This was considered by several contributors. Wider use of the qualitative 'spot test' for paraquat, with positive and negative controls, or the development of a more rapid and sensitive assay, perhaps using fluro- and enzyme-immunoassay should be investigated.[14] Work was presented aimed both at validating qualitative results of the 'spot test' for paraquat and extending the paraquat prognosis curve of Proudfoot *et al.*[21] beyond 24 h.[15]

Dr N. Bateman reviewed the efficacy of a wide range of pharmacological treatments in paraquat poisoning.[22] As yet there is no convincing evidence of benefit from the use of superoxide dismutase, propranolol, Vitamin E, ascorbic acid, riboflavin, niacin, desferrioxamine, selenium, clofibrate, acetylcysteine or corticosteroids. Attention was again drawn to the lack of both clinical trials data and information concerning plasma paraquat levels in many of the published papers. The ideal pharmacological antagonist for paraquat seems as far away as ever.

Dr M Williams reported the clinical course of five patients poisoned with paraquat who had received lung irradiation, and reviewed the literature concerning patients recovering from paraquat lung without active therapy.[23] Although the outcome of the five patients irradiated was not encouraging (four out of five died), attention was drawn to the number of patients that would be necessary to evaluate scientifically such a treatment, and the poor quality of published material in the scientific press.

A report of an immunosuppressant regimen[24] to reduce the acute alveolitis caused by paraquat may be read with similar limitations in mind.[25,26] Only 25 of Addo and Poon-King's 72 patients had plasma concentrations of paraquat measured. Although it is true to say that in six of these cases insignificant amounts of paraquat were detected, of the remaining 19 patients, seven lived despite the chances of survival, assessed from the survival curves of Hart *et al.*[27], being 30% or less. It is possible that in less severely poisoned patients, the use of immunosuppressives might be of value, though most physicians would feel that more detailed research is required before cyclophosphamide treatment can be recommended. Animal data presented at the Symposium[28] is not encouraging however, since no benefit was noted unless cyclophosphamide and dexamethasone were administered for 48 h prior to dosing.

The epidemiology and clinical features of paraquat poisoning are now well documented. There was wide agreement at the Symposium that there is at present no effective treatment for those severely poisoned individuals who have ingested substantial amounts of a concentrated formulation of paraquat. Equally, those who ingest less than a sachet of one of the granular preparations will survive even without treatment. In the middle are the small number of patients, at least in Europe, who might benefit from the use of prolonged haemoperfusion or other treatments. However, the number of patients required to evaluate prospectively such treatment are not available at any single European centre and therefore multicentre-studies are necessary. Until these trials are complete the recommendation that the concentration of the liquid preparations should be reduced is worthy of full consideration by the manufacturers and distributors.

It is probable that clinicians will continue to employ methods to decrease the absorption and increase the elimination of paraquat, even though there is no definite evidence of benefit, simply because a potentially fatal condition stimulates the innate desire of many doctors to 'do something'. At present in the majority of severely poisoned patients, attention could be more profitably directed to providing better terminal care.[10]

In summary, although ten years have elapsed since the first Symposium, the treatment of paraquat poisoning is no more satisfactory now than it was then. A decade ago haemoperfusion was thought to hold out the best promise but this has not proved to be the case. Aside from the preventive measures mentioned above, a greater understanding of the biochemical mechanisms of paraquat toxicity, together with pharmacological research to produce an agent capable of reversing biochemical damage, or blocking uptake into the lungs, seem the most hopeful approaches to this difficult clinical problem.

We hope that these proceedings stimulate further discussion and research.

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Human Toxicol. (1987), **6**, 7–11

Uses and Usefulness of Paraquat

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1 Paraquat was discovered in 1955 and introduced to the market place in 1962. During the 23 years between introduction and the present day numerous successful practical uses of the herbicide have been developed. In addition the characteristics of the chemical have allowed significant changes to be made in the ways that some crops are grown.
2 Paraquat is a relatively non-selective foliage-applied contact herbicide. It is inactivated on contact with almost all naturally occurring soils and it was this property, perhaps above all others, that provided the greatest breakthrough in chemical weed control at the time of its discovery.
3 Inactivation on contact with soil means that no biologically active residues remain in the soil, thus allowing planting or sowing to be carried out almost immediately after spraying. Although the non-systemic (contact) property of paraquat makes it less than ideal for the long-term control of perennial weeds, the same property is of real advantage when parts of crop plants are sprayed accidentally, for usually only the part receiving the spray is affected.
4 Total annual usage of all herbicides in agriculture and horticulture in England and Wales, UK, over the period of 1980–1983 has been estimated at 26 360 tonnes used on $12\,402 \times 10^3$ ha (1 hectare $= 1 \times 10^4$ m^2). For paraquat (not including its mixtures with diquat and monolinuron) 270 tonnes were sprayed over 392 218 ha/year. It is estimated from sales records that in Europe 5×10^6 ha are sprayed annually with paraquat.
5 The paper reviews the need for the use of herbicides and the properties that are important for particular crop–weed situations, but concentrates on the properties of paraquat that make it an essential agent of weed control in many areas of agriculture, horticulture and forestry.

Introduction

Weeds have existed as long as man but it was the introduction of rotation, after the enclosure of land, that made weed control an important element of efficient husbandry. By the mid-nineteenth century the cleaning crops of turnips and potatoes provided years in the rotation when weed control was possible by using hand labour. Later, when that became less economic, various mechanical devices, powered at first by animals and then by engines, were invented. The plough, first used in the UK before the Romans came, remained throughout this period a major weapon in weed control through its ability to bury growing weeds to depths from which it was difficult for them to emerge (Roberts, 1982).

Although several inorganic chemicals were in use for weed control early in the twentieth century and in the 1930s some organics were introduced for weed control in cereals, the real story of weed control by the use of chemicals did not begin until after World War II when the release of 4-chloro-2-methylphenoxyacetic acid (MCPA) and 2,4-dichlorophenoxyacetic acid (2,4-D) began a real revolution (Kirby, 1980). These herbicides were revolutionary because they were selective and gave control of many broad-leaved weeds in growing cereal crops. Quite suddenly crops (cereals) that had been the dirty crops of rotations because of the impossibility of weeding them, became, potentially, the cleaning crops. Although that dream was never realized fully, there was sufficient promise for some agronomists to begin to question the need for the plough.

Discovery of new herbicides

The success of the early phenoxyacetic acid herbicides triggered an enormous effort by the chemical industry to discover and develop chemicals with properties that allowed successful chemical weed control

in other crops. The approach was rewarded and in the UK there was an increase from 11 chemicals (104 products) approved in 1958 to 44 (277 products) 10 years later and 73 (450 products) by 1975 (Roberts, 1982). Paraquat (1,1′-dimethyl-4,4′-bipyridylium) was discovered in 1955 and brought to the marketplace in 1962. A monograph of the bipyridinium herbicides has been published (Summers, 1980).

Properties of herbicides

A much fuller review of the properties of herbicides is available in Roberts (1982).

Selectivity
Some herbicides are selective, that is, they may safely be sprayed at a recommended dose on mixtures of crops and weeds. The crop is not or is scarcely affected but the weeds are killed or seriously debilitated. Other herbicides are non-selective and are used either when the crop is absent or with methods which protect the crop physically. Paraquat is relatively non-selective, killing a wide range of annual grass and dicot weeds and the tops of established perennial weeds (Anon., 1984).

Modes of activity
Some herbicides are only effective in the soil or on the soil surface since they enter plants, principally, through the roots or emerging shoots (soil-active herbicides). Some of these may have long residual activity. Yet other materials are best applied to the foliage of weeds, but again these compounds divide into two groups: those which enter the leaves and thence the long-distance phloem transport system (foliage-applied translocated herbicides) and those which enter the leaves but are not exported from them (foliage-applied contact herbicides). As occurs in every classification there are herbicides which fall into more than one category but paraquat is, save under some very extreme circumstances, a foliage-applied contact herbicide.

Persistence
Persistence of herbicides in plants, soil and the environment also varies and, environmental implications apart, differences in persistence can be exploited in practice. Lack of persistence may arise because the molecule is degraded rapidly by, for example, microbial activity or sunlight or because the molecule is made unavailable for significant biological activity due to adsorption in the soil (or in the plant). Paraquat is broken down rapidly in sunlight and is so strongly adsorbed by clays and, to a lesser degree, by organic matter that it becomes biologically inactive on contact with most soils (Calderbank, 1968). This last property, as we shall see, provides, above all others, the key to the usefulness of paraquat.

Rainfastness
Many foliage-applied herbicides are liable to be washed off leaves if rain falls within a few hours of spraying with a consequent loss of effectiveness and money. Paraquat, however, is rainfast within minutes of application. This property reduces the operator's dependence on weather and allows great precision in the timing of applications.

Mode of action
Photosynthesis, that takes place in the green parts of plants when they are irradiated with sunlight, generates electrons which reduce the paraquat ion to a free radical which is rapidly reoxidized. During the reoxidization a superoxide is generated and this damages membranes and cytoplasm and leads to rapid death of cells (Calderbank, 1968).

Summary

Paraquat is a relatively non-selective rainfast foliage-applied contact herbicide with undetectable biologically active persistence in almost all soils. Its ability to cause rapid kill is dependent on the photosynthetic activity of plants.

Usefulness of paraquat

Figure 1 shows, diagrammatically, 12 of the situations in which farmers and growers seek to effect weed control. Paraquat is of no use for any of the models in column A, simply because the weed is buried in the soil and the herbicide cannot reach the target. However, where weed seedlings are emerged and the grower wishes to sow or plant a crop as soon as possible after controlling the weeds (B1) the properties of paraquat are ideal: kill is assured and the herbicide leaves no biologically active residue. This model (B1) has another context, one where the weeds are not seedlings but established plants that may include crop plants but where, after kill of all vegetation, either cultivation or direct drilling or planting of a new crop may follow very shortly after paraquat is applied. Again it is the lack of biologically active residues that permits almost immediate sowing or planting.

Because paraquat is not translocated, it is not the first-choice herbicide for perennial weed control (C1). The more recently introduced glyphosate [*N*-(phosphonomethyl)glycine] shares with paraquat and diquat the property of being biologically inactive in soil but glyphosate is a foliage-applied translocated herbicide. Nevertheless, paraquat sprayed on to the foliage of perennial weeds acts as a chemical

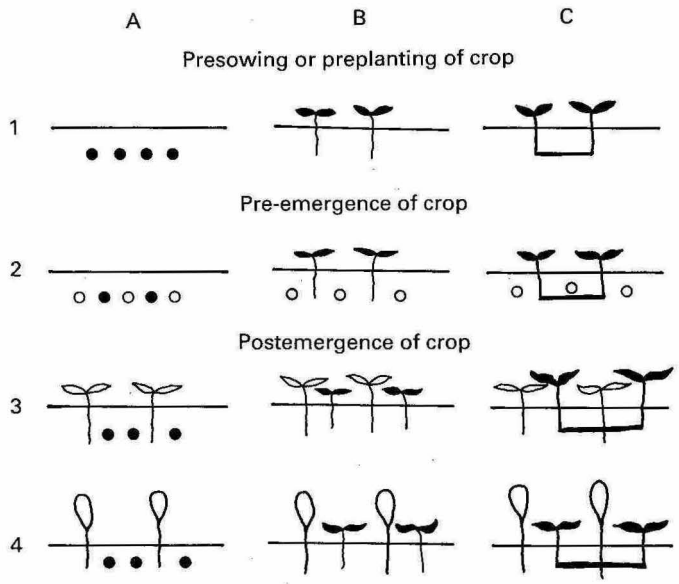

Figure 1 Diagrams illustrating 12 crop–weed situations. Columns: A, weeds present as seeds; B, weeds present as emerged seedlings; C, weeds present as perennials. Rows: 1, crop not yet sown or planted; 2, crop sown, but not yet emerged; 3, crop seedlings emerged; 4, crop perennial, often woody. • = weed seed; ○ = crop seed; = weed seedling; = crop seedling; = crop plant; = perennial weed [after H. A. Roberts (1982) Weed Control Handbook, vol. I, *Principles*, 7th edn. Oxford: Blackwell Scientific Publications]

scythe and destroys the above-ground parts of the weed and the use of herbicide on non-cropped land relies on this property. Regular applications of paraquat can lead, through attrition, to the control of perennial weeds.

In situations where the crop has been sown, weeds have emerged but the crop has not (B2, Figure 1), paraquat becomes a crucially important herbicide in the armoury. Yet again because of the speed of the inactivation process weeds can be killed only hours before the seedling crop plants emerge, thus giving the latter maximum competitive advantage. Similarly, areas planted to bulbs may be sprayed up to 3 days before the bulbs emerge (and again at the end of the growth cycle of the bulbs when all green foliage has disappeared). Care must, however, be exercised when the bulbs are grown on very sandy soils for the inactivation process may not be as effective as on heavier soils. In hops weed control is also possible before the plants emerge, in lucerne before the crop commences spring growth or after a harvest has been taken when little leaf is present. Perhaps the extreme examples of pre-emergence spraying with paraquat is with potatoes where up to 40% emergence of main-crop potatoes can be permitted before spraying. The emerged potato shoots are damaged but the resilience of the plant with its storage organ below ground, coupled with the failure of paraquat to be translocated down to the critical below-ground organs, allows recovery and makes ultimate economic sense because the crop emerges into what is effectively a weed-free environment. A foliage-applied non-selective translocated herbicide would be useless for such a situation.

Where the crop has emerged, the non-selectivity of paraquat precludes its use as an overall spray of both crop and weed. However, when crops are grown in rows it is possible, by using guarded no-drift sprayers, to kill weeds between the rows with paraquat (B3, Figure 1). Slight accidents where odd leaves of the crop plants are sprayed are not critical because the contact action means that only the sprayed leaves are killed. A rather more sophisticated practice, but one that depends on the same principles, has been developed for use in strawberries. The production of runners each year is a nuisance in a strawberry crop grown for fruit. By using carefully directed guarded sprays it is possible to kill the daughter plants with paraquat as the agent. Lack of translocation means that the mother plants are not affected by the spray and the adsorption of the chemical by the soil prevents leaching and possible damage to roots.

When crop plants are perennial and become woody with the lower parts of the stem completely covered in dead bark herbaceous weeds may be controlled safely with paraquat because the herbicide does not penetrate bark readily; it is adsorbed on to dead organic matter. This natural protection of the

crop has allowed the development of uses of paraquat for weed control in top fruit, in forestry and in vines (B4, C4; Figure 1). The use of paraquat to control unwanted suckers in vines is based on the principles, already described, for runner control in strawberries. Although bark is a useful physical defence against the penetration of paraquat, it is not wise nor standard practice to spray the bases of crop trees deliberately but accidental contamination, particularly when trees are in dormancy, has a considerable safety margin.

Until quite recently, the preparation of land for sowing or planting a crop was by ploughing and extensive cultivation of the soil. For a variety of reasons, many of them not directly relevant to this paper, the need to treat soil in this way was challenged and analyses of real needs were made from first principles. First, at the end of the life of any crop there is usually a residue of live and dead rubbish, some of it of crop origin and some of it representing weed material which has persisted beyond harvest. If these materials can be destroyed other than by ploughing then the plough is not required. Secondly, to establish a crop from seed, the physical structure of the soil must be suitable for the process of germination, emergence and subsequent growth. One of the aims of mechanical cultivation was to produce a 'tilth', although many soils which have grown crops already have an excellent structure at least in the uppermost layer. Thirdly, crop seedlings should, ideally, emerge into a weed-free environment. Cultivation is but a very temporary way of achieving this aim; herbicides are much more effective.

Against this background exciting research programmes, practical and fundamental, were initiated. The extreme variant, termed direct drilling, involves simply the effective clearance of old crop residues and weeds followed by the sowing of the seed of the new crop either directly on to the surface or inserted mechanically at a predetermined depth. This technique is energy conserving, very rapid and does not disturb the soil profile. Heavy machinery, which tends to destroy soil structure by compaction, is not needed.

The success of direct drilling varies with soil type (Anon., n.d.) and it is not successful universally.

Table 1 Summary of uses of paraquat

Lucerne	Minimum cultivation
Bulbs	Direct drilling
Potato	Stubble treatments
Row crops	Killing grassland before ploughing
Soft fruit	Forest nurseries
Hops	Forest plantations
Vines	Non-cropped land
Top fruit	

Table 2 Estimated annual use of paraquat over the years 1980–1983 in England and Wales, UK

Crop type	*ha/year*
Cereals	179 628
Grass	91 943
Other arable	76 138
Vegetables, bulbs	20 995
Top fruit	8894
Soft fruit	5995
Hops	4765
Hardy nursery stock	3706
Protected crops	154
Total	392 218

Values are spray-hectares [J. M. A. Sly (1985). Pesticide usage survey report (preliminary) 41. Review of usage of pesticides in agriculture and horticulture in England and Wales 1980–1983. Ministry of Agriculture, Fisheries and Food, London]

In consequence, a series of other techniques referred to as minimum or reduced cultivations have been developed. For both direct drilling and minimum cultivation a wide range of equipment and systems has been developed. Further information about the science and the practice of this whole area is available (e.g. Halliday, 1975; Allen, 1981; Butterworth, 1985) and comparisons have been made of the relative productivity of the systems (Matthews, 1975). Direct drilling a crop takes only 17.3% of the time that ploughing and cultivation would need.

This over-simplified picture of the cultivation revolution has been painted because its success has depended, although not exclusively, on the properties of paraquat; in particular, the speed of action, rainfastness, lack of selectivity and, above all, the non-residual activity of this herbicide have been crucial.

Use and uses

Most of the uses of paraquat have been identified in the previous section but they are presented as a list in Table 1. Two leaflets published by Plant Protection Division of ICI are particularly valuable as general accounts of the uses and usefulness of paraquat (Anon., 1981, 1983).

Paraquat is used at rates of between 0.7 and 8.5 litres of Gramoxone (the commercial product)/ha (1 hectare = 1×10^4 m^2) which is equivalent to about 14–170 g of paraquat/ha. In England and Wales, UK, over the period 1980–1983 it has been estimated that paraquat was sprayed on 392 218 h/year (Sly, 1985). Estimates from sales records suggest that in Europe 5×10^6 ha are sprayed annually with paraquat. In Table 2 is given a breakdown of the annual use in England and Wales; equivalent details for Europe as a whole do not appear to be available readily.

Postscript

I have attempted in this paper to illustrate the usefulness of paraquat and to show how its uses depend on the combinations of properties which are unique to the bipyridilium herbicides. The particular advantage of paraquat over diquat is the significantly greater ability of paraquat to control grass weeds.

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Paraquat — a Review of Safety in Agricultural and Horticultural Use

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1 Over the past 20 years plus that paraquat has been used throughout the world, it has enjoyed an excellent safety record when used normally and for its intended purpose.
2 Its safety record is explained by the following reasons: (i) inhalational exposure during normal use is not significant toxicologically; (ii) dermal exposure predominates during normal use; (iii) intact human skin provides a very good barrier against penetration by paraquat.
3 Its safety record has been confirmed by several field studies, which have assessed exposure and health of workers, who have used paraquat for short and longer periods of time. The unanimous conclusions of the studies is that exposure to paraquat does not result in any acute or chronic adverse health effects.
4 Minor and reversible injuries to the skin, eyes, nose and nails do occur and probably result from overexposure to the extremely irritant concentrated formulations. Most of these effects can be avoided using ordinary personal hygiene.
5 There have been a few anecdotal cases reported in the literature when dermal absorption of paraquat has genuinely occurred and led to serious health effects. In all cases prolonged exposure to concentrated paraquat solutions has been involved resulting in severe and extensive skin damage, with removal of the barrier and absorption of lethal amounts of the chemical.
6 Those cases involving exposure to concentrated paraquat solutions emphasise the need to handle such formulations, for example 'Gramoxone', with case and ensure that the spray solution is correctly made up—at a dilution of at least 1 part 'Gramoxone' to 40 parts water.

Introduction

Paraquat was first introduced as a broad spectrum contact herbicide in 1962. Since then, sales of the herbicide have expanded throughout the world, so that it is now used in over 130 countries. Several formulations are available, but the most common is 'Gramoxone', an aqueous concentrate containing 200 g paraquat ion per litre. Prior to application the concentrated formulation is diluted with water at least 40 times and very often 100 to 200 times to form a spray solution. The spray may be applied by hand-held or vehicle-mounted sprayers or by air.

Over the 20 years plus it has been sold, it is our experience that the normal use of paraquat has not led to serious health injury or fatality with workers using the product. Normal use does not necessarily equate with recommended use, since it may also involve minor and predictable deviations from recommended use. These deviations include blowing out blockages in nozzles, leaking sprayers, or spillages. Furthermore normal use does not always involve the use of protective clothing or equipment.

The purpose of this review is to examine the evidence for paraquat's safety in normal use and to explain the reason for it. It is not the aim of this paper, to review its abuse, with which toxicological incidents are usually associated and may be defined as a use of the chemical for which it was never intended, for example ingestion, injection or deliberate dermal application. However misuse of paraquat, which may be defined as use of the product associated with gross deviation from label recommendations, is addressed.

Exposure during normal use

Several exposure studies with paraquat have been carried out under actual field spraying conditions, using hand-held sprayers as well as tractor and aerial application. The exposure to covered and uncovered skin was determined by chemical analysis of patches placed on different body regions.[1] Inhalational exposure (including oral exposure) was established

Table 1 Worker exposure to paraquat

Application method	*Exposure to uncovered skin (mg h^{-1})*	*Exposure to covered and uncovered skin (mg h^{-1})*	*Inhalational* exposure (mg h^{-1})*	*Reference*
Hand-held (Knapsack)	0–12	12–170	$(0–5) \times 10^{-3}$	Chester & Woollen[2]
Vehicle-mounted	0.01–3.4	–	$(0–2) \times 10^{-3}$	Staiff *et al.*[3]
	3.6 –50.4	12–169	$(0–70) \times 10^{-3}$	Wojek *et al.*[4]
Aerial-Flagger	0.1 – 2.4	–	$(0–47) \times 10^{-3}$	Chester & Ward[5]
Pilot	0.05–0.26	–	$(0–0.6) \times 10^{-3}$	

* Assumes a lung ventilation of 1.8 m^3 h^{-1}

using personal air sampling equipment and the air concentration of different particle sizes of paraquat was determined. The data from these studies are summarised in Table 1.

It is evident from these results that skin exposure represents by far the most significant route of absorption, since inhalation exposure is approximately three orders of magnitude less than skin exposure. Furthermore inhalational exposure of paraquat is toxicologically insignificant. The Time Weighted Average Threshold Limit Value (TLV) for paraquat is currently 0.1 mg m^{-3} (American Conference of Governmental Industrial Hygienist 1982/3)[6] equivalent to 0.18 mg h^{-1}*, which is much greater than the inhalational exposure measured during paraquat use. Also the TLV assumes inhalation of respirable particle (1–7 μm mean diameter) only, whereas the figures quoted in Table 1 represent total inhalational exposure, including respirable and non-respirable droplets. It is worth noting that Chester & Ward[5] reported that no respirable droplets of paraquat could be detected during aerial application.

This very low inhalational exposure is explained by the fact that paraquat is non-volatile and applied as a spray containing relatively large droplets which are downwardly directed. Application of very fine droplets, which could drift, is not recommended for paraquat use. The insignificance of inhalational exposure and the significance of dermal exposure during herbicide application has been confirmed in a recent study by the British Agrochemicals Association.[7]

Dermal absorption

Since the above data leads us to the conclusion that skin exposure is the important route of absorption to consider, understanding of the skin penetration of paraquat is necessary to evaluate its safety in use. Knowledge of dermal penetration of chemicals has improved in recent years and several laboratory techniques to measure it are currently available.[8]

The ability of paraquat to penetrate skin has been studied in the laboratory using an *in vitro* technique with both animal and human skin.[9] The technique involves insertion of a section of epidermis (from human or animal skin) between two glass diffusion chambers (see Figure 1). Human epidermis is obtained by immersing post-mortem samples of abdominal skin in water at 60°C for 40–45 s. Animal epidermal samples are prepared using a similar technique involving the use of chemical reagents. With the sample in place, between the chambers and supported on a metal grid, a solution of chemical is introduced into the 'Donor Chamber'.

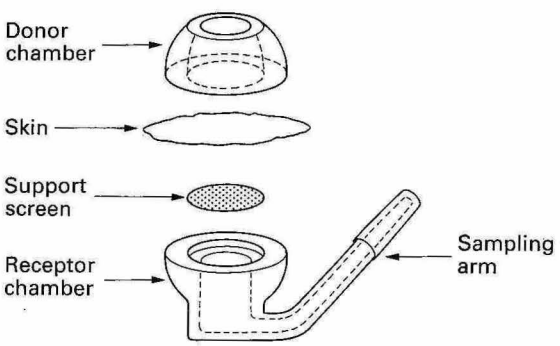

Figure 1 *In vitro* method for assessment of skin penetration by chemicals

The 'Receptor Chamber', containing water and/or suitable solvent is then sampled at different time intervals and the samples analysed for chemical content. The analysis provides information on the amount of chemical which has penetrated the epidermal section over a given period of time. By knowing

the surface area of contact, the rate of skin penetration, in terms of amount (μg) per unit area (cm^2) per unit time (h) can be calculated. The permeability constant (units of cm h^{-1}) can also be calculated and represents the rate of penetration divided by the concentration of chemical applied.

Using this technique it has been shown that intact human skin is a very good barrier to paraquat in solution, at concentrations equivalent to those used in sprays applied in practice. Furthermore, Walker *et al.*[9] showed that the permeability of skin to paraquat is much less than the permeability of skin to many other chemicals. These data are summarised in Table 2 below.

Confirmation of these *in vitro* results, has been provided by Wester *et al.*[10], who examined percutaneous penetration of paraquat using human subjects. The results of this human study, which also used a spray strength solution of the chemical, gave a similar rate of penetration to the *in vitro* model.

Walker *et al.*[9] also showed that human skin is much less permeable to paraquat than the skin of several animals (Table 3). Thus by comparing the figures in the right-hand column we find for example that rat skin is 40 × and rabbit skin is 130 × more permeable to paraquat than human skin. From this it is clear that the dermal LD_{50} carried out on animals (usually rat and rabbit) gives a large overestimate of the potential hazard of paraquat to man by this route.

In summary the importance of the dermal route of absorption during normal use together with the excellence of the skin as a barrier help to explain why paraquat is safe to use. This explanation has been reinforced by the results of field surveys examining the health of workers exposed to paraquat.

Field studies with spray operators

Swan[11] described two of the earliest studies demonstrating the safety in use of paraquat. The two studies were conducted in Malaysia, where exposure tends to be heavy and the use of paraquat is intense. Clothing worn consisted of shirt or singlet, long trousers (tucked into the socks) and variety of footwear ranging from open sandals to leather boots. Each study involved exposure of 6 workers to the herbicide over a 12-week period, (6 working days per week) and the native workers (2 Chinese, 2 Malaysian and 2 Indian) were medically assessed before, during and after each spraying trial.

Table 2 Permeability of human skin to chemicals[9]

Chemicals	*Vehicle*	*Permeability constant ($cm\ h^{-1} \times 10^5$)*	*Lag time (h)*
Toluene	Ethanol/water 1:1	2100	0.06
HCN	Water	1000	0.05
Cyanide ion	Water	35	1.5
Hexachlorophene	pH 8.8 Aqueous	220	22
Water	Water	100	0.4
Progesterone	Water	150	2.5
Cortisone	Water	1	220
Paraquat	Water	0.75	24

Table 3 Permeability of animal and human skin to paraquat

Species	*Water permeability (Perm Const. $cm\ h^{-1} \times 10^{-5}$)*	*Paraquat permeability (Perm. Const. $cm\ h^{-1} \times 10^{-5}$)*	*Permeability increase relative to man*
Man	93	0.75	—
Rat	103	27.2*	40
Hairless rat	130	35.3*	50
Nude rat	152	35.5*	50
Mouse	144	97.2*	135
Hairless mouse	351	1065*	1460
Rabbit	255*	79.9*	130
Guinea pig	442*	19.6*	270

* Significantly different from human

None of the workers showed any serious adverse health effects which could be attributed to paraquat exposure. In particular no worker exhibited any lung abnormality detectable by chest radiography.

Approximately half the number of workers had some irritation of the eyes or skin at some time during the 12-week exposure. With the exception of two cases of scrotal dermatitis, produced by exceptionally prolonged contact with the chemical, all these effects were mild and cleared rapidly within 24 to 48 h. Only one man of the twelve complained of epistaxis. He had been spraying on a steep hillside downwind of the other workers. The nasal mucosa was very congested, but returned to normal after a few days.

Urine levels of paraquat were measured throughout the study. Most of the levels fell below 0.1 $\mu g\ ml^{-1}$ of paraquat ion with a maximum recorded value of 0.37 $\mu g\ ml^{-1}$. The author compared these levels with urinary levels from patients, who had swallowed paraquat accidentally or with suicidal intent. In two cases which survived one (Leading article BMJ[13]) had a urine concentration of 44 $\mu g\ ml^{-1}$ in the first 24 h falling to 5 $\mu g\ ml^{-1}$ after 48 h. In the other[12] the urine level was measured at 148 $\mu g\ ml^{-1}$ some hours after ingestion. This patient, who was thought to have swallowed 2 g of paraquat ion, also survived.

Swan concluded that 'ordinary care in personal hygiene is sufficient to prevent any hazard from surface injury or from systemic absorption'.

In another study on the exposure of spray operators to paraquat in Ireland, Hogarty[14] points out that no fatalities, from spraying in accordance with recommended practice, have been reported. This is in sharp contrast with cases involving ingestion of the chemical.

Hogarty showed that the number of spray droplets produced, which were less than 16 μm diameter was very small during application and that the number of respirable droplets was about 0.001% of the total number of droplets. On measuring air and urine concentrations of paraquat, Hogarty could not detect any airborne paraquat and urine samples were negative for paraquat. Medical tests indicated that spraying paraquat had had no effect on the health of the three workers involved and that no paraquat was likely to have been inhaled or ingested during the trial.

Hogarty concluded that 'there is little or no risk attached to the use of paraquat dichloride as an agricultural herbicide, provided recommended methods of application are adhered to'.

This conclusion was largely supported by Hearn and Keir[15] who also demonstrated the development of local nail effects in 53 out of 296 workers on Trinidad sugar estates, but found no evidence of effects from systemic absorption. The dilutions of 'Gramoxone' were from 1:100 to 1:200 (i.e. from 0.2 to 0.1 per cent paraquat ion in the final spray solution).

More recently a survey of 36 paraquat dichloride formulation workers in England and Malaysia by Howard[16] also failed to shown any systemic effects from the dermal absorption of paraquat, although the incidence of local reactions indicated that the workers had been exposed to the compound in the formulating process. It is worth noting that this group included persons who had been exposed to paraquat for long periods of time (up to 12 years of workplace exposure) and there was no evidence of chronic skin problems nor of any effects on lungs or other organs.

Howard[17] also produced a detailed review of paraquat worker exposure in normal usage. He concludes that the available evidence supports the contention that systemic poisoning from recommended agricultural use does not occur.

However, on rare occasions during the last 20 years there have been incidents, reported in the literature,[18–23] in which extensive skin damage has led to increased dermal absorption and death from systematic paraquat poisoning. Without exception, these cases arose from gross misuse of the product. It must be stressed that contact with high concentrations of paraquat over a prolonged period, so as to cause extensive skin damage and removal of the barrier, is a prerequisite for the absorption of a lethal amount of paraquat. In two of the references cited (Jaros *et al.*[18] and Levin *et al.*[19]), workers had been using relatively high concentration sprays (4% and 2.8% paraquat ion respectively, which is specifically against the manufacturer's recommendations. The concentrated sprays produced severe and extensive skin damage in both cases, and death resulted from dermal absorption of paraquat.

The effect of prolonged contact of concentrated paraquat solution on the skin was also demonstrated by Athanaselis *et al.*[20] Once again the concentration of paraquat spray solution used (probably in excess of 1–2% paraquat ion) was far higher than the maximum recommended by the manufacturer (0.5% w/v paraquat ion).[24]

The case described by Waight[21] resulted from breakage of a bottle containing concentrated paraquat solution carried in the patient's pocket and subsequent prolonged contact of this on the skin. In the other two cases,[22,23] undiluted 'Gramoxone' was used to kill body lice by applying liberally to the scrotal area—clearly a form of abuse.

In the above cases, there is little doubt that paraquat poisoning took place by dermal penetration. In many cases however the route of absorption is in doubt, mainly because a patient has denied swallowing the product. In such cases, for example that described by Newhouse *et al.*,[25] a diagnosis of dermal poisoning is speculated. However careful analysis of these cases, can reveal the presence of symptoms, which

are consistent with ingestion despite denial by the patient. In the case described by Newhouse *et al.*, the patient exhibited nausea and vomiting, which are far more likely to have occurred from the ingestion of paraquat than from dermal contact.

Safety of paraquat—long-term use

It has often been reported in the literature that ingestion of paraquat may lead to accumulation of the chemical into the lung with the consequent result of lung damage. Due to its lung damaging potential, concern has arisen as to whether long-term exposure to paraquat will also result in lung accumulation and damage.

The accumulation of paraquat into the lung is both time and energy dependent and will obey saturation kinetics.[26] This means that as the concentration of paraquat in the plasma falls, the rate of uptake into the lung will also fall. At the same time as paraquat is taken up into the lung, it is also being removed from the lung. A plasma concentration will eventually be reached, when the rate at which paraquat enters the lung will be equal to the rate at which it is removed and at this concentration no lung accumulation will occur. For animal models, e.g. the rat, this concentration can be calculated to be between 0.2 and 0.5 $\mu g\ ml^{-1}$.[27] Since laboratory studies have shown that human lung behaves similarly towards paraquat as rat lung,[28] it is reasonable to conclude that continuous plasma levels of between 0.2 and 0.5 $\mu g\ ml^{-1}$ of paraquat ion will not lead to lung accumulation and damage in man.

Further evidence of a plasma concentration threshold, below which lung accumulation and damage will not occur is available from animal studies. Rats exposed to an aerosol of paraquat (particle size $< 3\ \mu m$) containing 0.1 μg paraquat ion/litre for 6 hours per day, five days per week for three weeks do not develop lung damage.[29] Furthermore, although lung levels rose during the first few exposures, they eventually reached a stable level of 1 $\mu g\ g^{-1}$ of lung tissue. Rats fed on a diet containing 150 mg kg^{-1} of paraquat did not develop lung damage as defined under light microscopy and the lung levels did not exceed 0.5 $\mu g\ g^{-1}$ of lung.[30]

In occupational use of paraquat, although plasma concentrations have not been directly measured, urine concentrations have been reported in two studies. Swan[11] found that urine concentrations usually contained less than 0.1 $\mu g\ ml^{-1}$ of paraquat ion with a maximum recorded value of 0.37 $\mu g\ ml^{-1}$. Chester & Woollen[2] found urine levels were usually below 0.05 $\mu g\ ml^{-1}$ paraquat ion (maximum of 0.76 $\mu g\ ml^{-1}$).

It is well recognised that paraquat is excreted unchanged in the urine. With normal renal function the rate of excretion is greater than the rate of clearance by glomerular filtration (Davies).[31] Therefore it is reasonable to assume that the concentration of paraquat in urine will greatly exceed the plasma from repeated exposure, and that plasma paraquat concentrations in workers are likely to be much lower than the urine concentrations measured and probably non-detectable ($< 0.01\ \mu g/ml$). Under these circumstances lung accumulation and resultant lung damage will not occur.

It was not surprising, therefore, that when Howard *et al.*[32] evaluated the health of 27 agricultural workers, who had a long history of paraquat exposure in Malaysia (average 5.3 years exposure), no difference was observed between the health of these workers and the health of the two non-exposed control groups (factory and general estate workers). In particular there was no difference in lung functions, including transfer factor, and no difference in blood biochemistry for hepatic and renal function. Howard concluded that the long-term exposure under Malaysian conditions did not result in any serious health effects.

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The Epidemiology and Prevention of Paraquat Poisoning

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1 In the UK there was an increase in the annual number of deaths associated with paraquat poisoning between 1966 and 1975. Since that time there has been little change in numbers.
2 High mortality is associated commonly with suicidal intent. Serious accidental poisoning from paraquat has never been frequent in the UK and there have been no deaths reported in children since 1977.
3 The National Poisons Information Service has monitored in detail all reports of paraquat poisoning since 1980. Of the 1074 cases recorded there were 209 deaths. In recent years serious poisoning has been more commonly associated with ingestion of concentrated products by males. Local exposure to paraquat has not resulted in systemic poisoning.
4 International data for paraquat poisoning is incomplete and difficult to compare. There is a scarcity of morbidity data at both international and national levels. Information obtained from Poison Control Centres indicates that paraquat poisoning occurs in many countries but detailed comparisons are hindered by lack of standardised methods of recording.
5 Various measures to prevent paraquat poisoning have been introduced. Their effectiveness has not been studied in detail. Some support is provided by the low incidence of serious accidental paraquat poisoning in the UK, but because of the suicidal nature of paraquat poisoning it is unlikely that current preventative measures will influence the number of deaths occurring each year.
6 Preventative measures against paraquat poisoning should be tailored to national needs, based on and assessed by epidemiological studies.

Introduction

The preceding papers have stressed both the importance of paraquat to agriculture, and its safety when correctly used. Paraquat is, nevertheless, toxic to man and this toxicity has been the subject of a great deal of attention in the scientific and 'lay' press. The first cases of paraquat poisoning occurred in 1964, in Ireland and New Zealand (Bullivant, 1966) and by 1970 some 600 fatalities had been reported in the world literature (IPCS, 1984). In spite of the interest, it remains a difficult task to describe the mortality and morbidity associated with paraquat poisoning in different countries in strict epidemiological terms. Such a description requires appropriate and comparable mortality and morbidity statistics. A recent review found that 'because of the different requirements or practices for notification or reporting of cases of poisoning in the many countries in which paraquat is used, the magnitude of the problem is difficult, if not impossible, to determine' (IPCS, 1984). We concur with this view after reviewing the information available from Poison Control Centres, routine sources of mortality and morbidity data and from scientific reports. The information available from these sources is presented and the measures aimed at preventing paraquat poisoning reviewed.

Sources of information

1. Hospital based surveys
The Home Accident Surveillance Scheme (HASS) records standardised data from a sample of twenty Accident and Emergency (A&E) departments in England and Wales on all types of home accidents (Consumer Safety Unit). A request was made for the number of admissions due to home accidents with weedkillers occurring during the period October 1982 to October 1984. In addition the results of an epidemiological study of acute poisoning cases attending twenty one A&E departments in England and Wales were examined (Murray, Francis & Thompson 1986).

2. Poison Control Centre reports
These reports include the results of a five-year surveillance of paraquat poisoning undertaken by the National Poisons Information Service (NPIS) and the

manufacturer (ICI plc) since 1980. Details of the methods used have been previously published (Hart & Bramley, 1983; Whitehead, Volans & Hart, 1984). In addition the results of a survey amongst European Poison Control Centres of the incidence of paraquat poisoning, undertaken by the secretary of the European Association of Poison Control Centres (EAPCC) (Wickstrøm, 1984) have been examined together with other information from Poison Control Centres given directly to the authors.

3. Mortality statistics

Statistics for England and Wales published in the *Pharmaceutical Journal* for 1966–1973 and by the Office of Population Censuses and Surveys (OPCS) for 1974–1984 have been used. Data was not published in 1981 in England and Wales due to industrial action.

For Scotland, statistics were obtained from the Annual Report of the Registrar General from 1967 to 1984.

4. Other sources

Information from the Agrochemical Poisoning Appraisal Panel (APAP) which is administered by the Health and Safety Executive to investigate reports of occupationally related pesticide poisonings together with information published in the scientific press has been analysed.

Morbidity from paraquat poisoning

1. Hospital based surveys

From October 1982 to October 1984, over 287,000 home accidents were reported to HASS. Of the 39 which were due to weedkillers only seven could be identified as containing paraquat. Four of these involved children under 2 years of age, but only one was admitted into hospital. Limitations in the HASS reporting system, for example fatalities not being included and trade names not always being recorded, may mean that this number of cases is an underestimate.

A preliminary report showed that over a period of one year 22 195 cases of acute poisoning attended A&E departments in England and Wales. Only 14 cases of exposure to paraquat were recorded (Murray *et al.*, 1986). The number of admissions to the hospitals in the study represent approximately 12.5% of all admissions in England and Wales. The total number of exposures due to paraquat may therefore be estimated at 112 but final figures are expected to be higher (J. Francis, personal communication).

A retrospective study of cases of self-poisoning presenting at the United Norwich Hospitals during the five-year period 1978–1982 found twelve admissions due to paraquat (Adams, 1986).

An important source of morbidity data, the Hospital-In-Patient enquiry (HIPE), fails to document admissions due to paraquat. This is because the International Classification of Diseases (ICD) used for coding the cause of admission has no specific code for paraquat. Any information would be contained in a general category, such as admission due to toxic effects of 'other substances chiefly non-medicinal as to source'.

Outside the UK we found no published national morbidity information concerning paraquat. A national study conducted by the Environmental Protection Agency in the United States concerning hospitalised pesticide poisonings failed to document any cases due to paraquat, even though 2954 admissions due to pesticides were reported in 1974 (G.R.A. and I., 1981).

We therefore concur with a recent report that there are no published national morbidity statistics for pesticides (Vale & Buckley 1986) and that this is particularly true for paraquat. For this reason Poison Control Centres have been identified as potential sources of 'morbidity data' (Brzezinski 1976; Volans & Wiseman, 1986).

2. Poison Control Centre (PCC) reports

(a) United Kingdom – National Poisons Information Service (NPIS). Over the period 1980 to 1985, more than 1000 cases of exposure to paraquat were reported to the NPIS (Table 1). 70% (760) of all cases involved ingestion. Other reported routes of exposure were inhalation (9.8%), skin contact (9.3%), eye contact (2.3%) and injection (0.7%). Of these routes only ingestion and injection led to symptoms of systemic poisoning, though one case of skin contact resulted in a positive urine test.

Of all the cases of ingestion 13% of patients were under five-years-old, 2% were aged between 5 and 12 years, and 85% were older than 12 years. Outcome of the incident was confirmed in 81% of cases (67% survival) by the attending physician, generally about four to five months after the incident. It was not possible to obtain complete follow-up because of difficulties in tracing patients who were not admitted into hospital.

The proportion of survivors having symptoms was estimated for 1984, when 74% of adults had symptoms whereas in the under 5 age group only one child (8.3%) had.

The Agrochemical Poisoning Appraisal Panel recorded three occupationally related paraquat poisonings in 1982.

Thus paraquat poisoning does not seem to represent a problem: to children, by skin and eye contact, inhalation, and through occupational contact.

Table 1 Paraquat cases notified to the NPIS over the years 1980–1985

Year	Total number of cases	Number of cases of ingestion	Age and outcome of ingestion cases: < 5 yrs S	D	NK	5 – 12 yrs S	D	NK	> 12 yrs S	D	NK	Number of deaths by ingestion	Total number of deaths
1980	152	121	11	—	3	—	—	1	54	37	15	37	37
1981	169	127	4	—	2	1	—	—	57	45	18	45	47
1982	223	154	16	—	5	—	—	1	78	38	16	38	41
1983	198	143	15	—	8	—	—	5	64	33	18	33	33
1984	189	132	12	—	9	3	—	1	58	32	17	32	32
1985*	143	83	9	—	8	1	—	1	26	19	19	19	19
Total	1074	760	67	—	35	5	—	9	337	204	103	204	209

S: Survival D: Death NK: Not known
* Provisional figures

Table 2 Cases of paraquat poisoning reported internationally

Country	Cases (fatalities in brackets) 1980	1981	1982	1983	1984	Source
UK	152 (37)	169 (47)	223 (41)	198 (33)	189 (32)	NPIS
England & Wales	(24)	NK	(31)	(36)	(31)	OPCS
Scotland	(6)	(12)	(9)	(5)	(9)	Registrar General
Denmark			(3 over 3 years)			Copenhagen PCC
France	90	106	83	NK	NK	Wickstrøm*
		27 (20)	—	—	—	Frelan 1983
Germany (West)			(8 from 1978–1983)			Wickstrøm*
Greece	25	49	65	85	80	Athens PCC
Eire	NK (13)	NK (4)	59 (9)	54 (14)	53 (7)	Dublin PCC
Netherlands	29	39	19	NK	NK	Wickstrøm*
Czechoslovakia			(2 to 3 per annum)			Wickstrøm*
Norway			(3 over 12 years)			Wickstrøm*
Poland	6 (3)	7 (0)	12 (10)	NK	NK	Wickstrøm*
Spain	NK	NK	7	NK	NK	Wickstrøm*
Sweden	1 (0)	2 (0)	0	0	0	Stockholm PCC
Switzerland	10 (1)	8 (2)	8 (1)	6 (3)	3 (2)	Zurich PCC
Israel	NK	(4)	(2)	(0)	(0)	Haifa PCC
Australia	NK	NK	11	8	10	Canberra PCC
Fiji	—	—	49 (30)	59 (33)	—	Groundar 1984
Japan					(1300)	Naito 1986
USA	NK	NK	NK	NK	153 (1)	AAPCC 1984

* Personal communication

(b) Other countries Cases of paraquat poisoning recorded over the period 1980–1984 are shown in Table 2. This shows that there are differences in the extent of paraquat poisoning with relatively little occurring in Sweden, Norway, Czechoslovakia and West Germany. However the comparability of these figures is not known because of the different methods of recording and following-up cases and nature of the services provided by the different countries. For example poison control centres in the United States accept enquiries from members of the public, unlike centres in the United Kingdom.

Mortality from paraquat poisoning

1. National mortality statistics

Figure 1 shows the number of fatalities recorded per year in England and Wales, Scotland and Eire for the period 1965–1984. In England and Wales, the first fatalities due to paraquat poisoning were recorded in 1966. Over the ten-year period to 1975, fatalities increased from 1 to 43 cases per annum with a rapid increase occurring between 1971 and 1975. Numbers since 1975—although fluctuating—have not changed significantly, 31 were recorded in 1984.

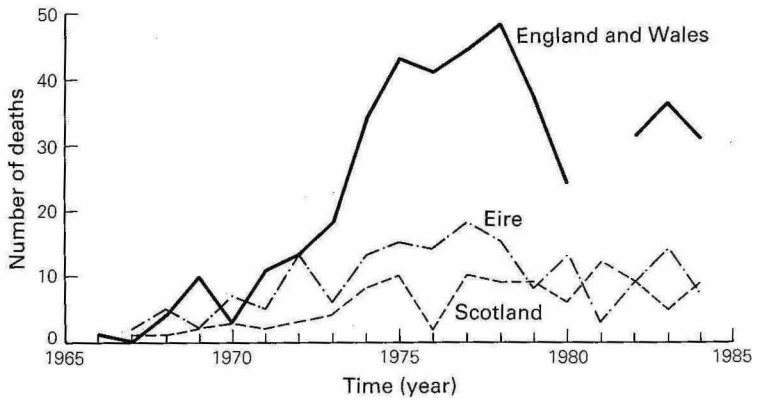

Figure 1 Deaths due to paraquat 1966–1984 for England and Wales, Scotland and Eire
Sources: England and Wales, Pharmaceutical Journal (1966–1973) OPCS DH4 Series (1974–1984).
Scotland, Annual Report of the Registrar General (1966– 1984).
Eire, Fitzgerald *et al.* 1978 (1967–1976). Dublin Poisons Unit (1977–1984).

For Scotland, the trend is similar to that for England and Wales. One case was recorded in 1967 rising to 10 cases in 1975, since when the numbers have remained relatively stable—9 were recorded in 1984.

For Eire, an increase from 1 to 13 fatalities per annum occurred between 1967 and 1972 but since then numbers have been fluctuating at 12 ± 4 per year.

A review of the status of paraquat poisoning in Eire between 1967 and 1976 (Fitzgerald, Barniville, Flanagan *et al.*, 1978) revealed that the mortality in terms of population was approximately seven and a half times that in Great Britain. Figure 2 shows the population-corrected incidence of paraquat poisoning in England and Wales, Scotland and Eire. It can be seen that the incidence of paraquat fatalities in Eire remains high, approximately four times that of England and Wales and twice that of Scotland.

Poisoning with solid and liquid substances in England and Wales remained fairly constant over the period 1973–1980 (Osselton, Blackmore, King *et al.*, 1984) but in recent years (1981–1983) a decline has occurred. Similar trends are seen for Scotland. Over these periods the proportion of deaths due to paraquat continued to increase. Thus, in England and Wales, paraquat has accounted for an average of 1.4 ± 0.2% of all poisonings with solid and liquid substances since 1975. Over the same period in Scotland it has accounted for an average of 2.3 ± 0.8% with a maximum of 3.78% being recorded in 1984.

There is thus no evidence to suggest that paraquat poisoning is becoming a less important cause of mortality in the UK.

Information on the intent of the poisoning is recorded at the inquest into the death and can either be 'suicidal', 'accidental' or 'not determined' whether suicidal or accidental. Figure 3 shows the total numbers of fatalities classified into these categories over the period 1966–1984 for England, Wales and Scotland. It can be seen that although the numbers recorded for suicidal intent follow very closely those of the total, numbers due to accidents remain below five per annum, with the exceptions of 1975 and 1976 (10 and 6 respectively). The number of not determined cases reached a maximum in 1977 (12 per annum) coincident with a decline in accidental deaths. However, the influence of this category on the number of accidental deaths remains difficult to interpret, and it is more likely that the number of suicidal deaths would be influenced by the 'not determined' category because of religious and other constraints in bringing in a verdict of suicide. It is clear from these figures that the rise in paraquat fatalities which occurred from the late 1960's to the early 1970's was due to an increase in the use of paraquat for suicide.

Of the 428 deaths recorded as due to paraquat, over the period 1966–1984 in England and Wales, 75% were male and 25% female. 77% of the suicidal deaths and 65% of accidental deaths over this period occurred in males. A similar sex distribution is found for the 105 recorded fatalities in Scotland; 74% of the total were male; 78% of suicides and 59% of accidental deaths were male.

Details regarding age of patient are not available from published mortality statistics which give broad age ranges. However, over the period 1968–1977 six paraquat fatalities occurred in British children under the age of ten; these were accidental in nature. For comparison over the same period 49 children (under

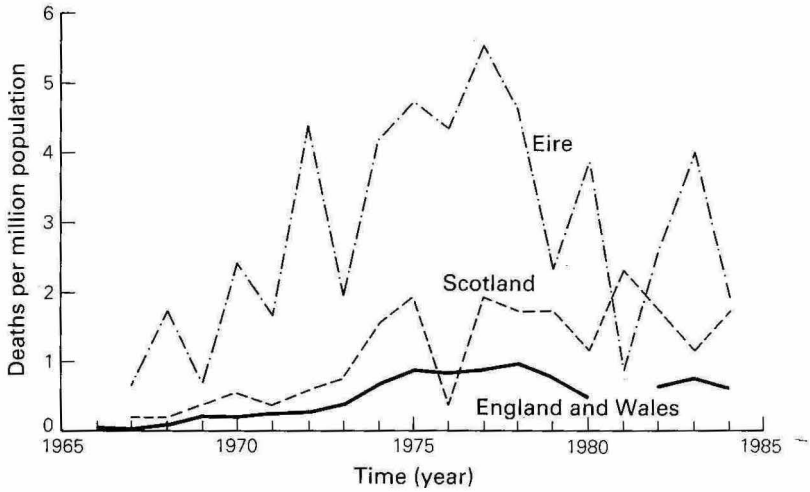

Figure 2 Deaths due to paraquat 1966–1984 per million population for England and Wales and Scotland
Sources: England and Wales, Pharmaceutical Journal (1966–1973). OPCS DH4 Series (1974–1984). Population Trends 42 1985.
Scotland, Annual Report of the Registrar General (1966–1984). Population Trends 42 1985.
Eire, Fitzgerald *et al.* 1978 (1967–1976). Report on Vital Statistics CSO Dublin 1982.

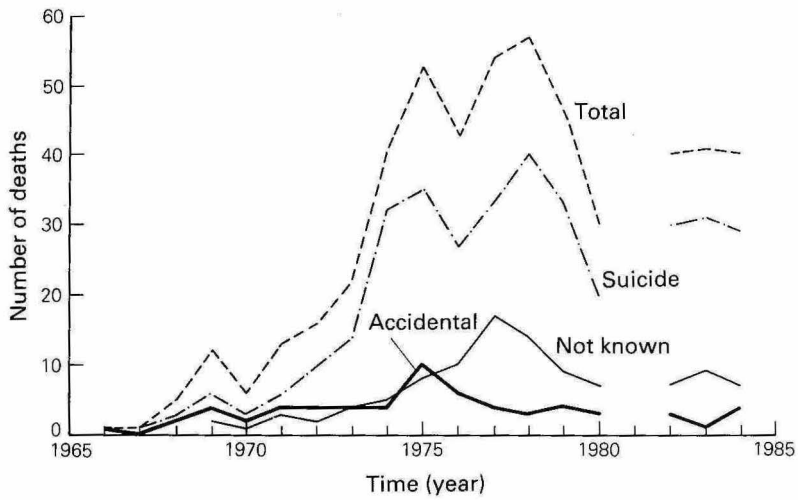

Figure 3 Deaths due to paraquat 1966–1983: Accidents vs suicide, for England, Wales and Scotland
Sources: England and Wales, Pharmaceutical Journal (1966–1973). OPCS DH4 Series (1974–1984).
Scotland, Annual Report of the Registrar General (1966– 1984).

ten) died as a result of accidental ingestion of tricyclic antidepressants (Frazer, 1980). Since 1977 there have been no reported deaths due to paraquat in this age group.

The Registrar General for Scotland was able to provide details of occupation in 79 of the 81 fatalities occurring from 1975 to 1984. Only in 13 cases (16%) was there any direct link between occupation and access to paraquat (e.g. farmer, market gardener, groundsman). In Eire it was found that a wide range of occupational types were involved in paraquat poisonings but that intentional poisoning was commonest among agrochemical workers (Fitzgerald *et al.* 1978).

2. Other countries

No national published mortality statistics listing paraquat were found. Data on mortality is published by the World Health Organisation, however only a broad categorisation of poisoning based on ICD codes is given, paraquat therefore is not listed. The same limitations were found with vital statistics available from individual countries.

Additional information regarding fatalities due to paraquat may be obtained from Poison Control Centres.

3. Poison Control Centre reports

a. United Kingdom—National Poisons Information Service. Of the 1074 cases of paraquat exposure reported to the NPIS, 209 cases proved fatal. There was a predominance of males (72%) and of deliberate intent (85%) involved in the fatalities (Table 3). The mean age for males was 44.6 (S.D. = 16.5) and 54.1 for females (S.D. = 14.2).

71% of fatalities involved concentrated liquid formulations (Table 3) and 22% granular formulations. There was a marked predominance of male fatalities involving the liquid formulations (78% male, 22% female) although there was no such difference with the granular products (54% male, 46% female).

Table 3 Type of product, intent and sex of patient involved in 209 fatalities reported to the NPIS (1980–1985)

	Accidental	*Deliberate*	*NK*
Liquid concentrate			
Male	4	100	12
Female	—	30	2
Total = 148			
Granular			
Male	3	21	1
Female	2	18	1
Total = 46			
NK			
Male	—	8	2
Female	1	1	3
Total = 15			
Totals: 209	10	178	21

Note: Liquid concentrate: Gramoxone, Dextrone, Gramonal, Cleensweep
Granular: Weedol, Pathclear

Of the 209 fatalities, 204 were due to ingestion of the product, two were due to injection, one intravenously and one intramuscularly and in three cases the route of exposure was not known.

Information was available as to the geographical distribution of 173 of the fatal cases. In absolute numbers most fatalities occurred in Greater London, West Midlands and Belfast. However, this could be due to the large populations and/or the presence of centres taking an interest in the treatment of paraquat poisoning. Figure 4 shows that, when corrected for population differences, there are disproportionately large numbers of fatalities (seven or more per million) occurring in Belfast, Devon, Cornwall, Norfolk, West Sussex and West Glamorgan—a pattern which probably reflects the scale of the agricultural industry in these areas.

Information regarding occupation was only available for 67 of the 209 fatalities. Of these 39% had occupations which gave ready access to concentrated paraquat products, the remaining occupations were varied, with no obvious relationship to agriculture.

There are differences between the number of fatalities reported to the NPIS and those recorded from death certificates in England, Wales and Scotland. Both sources of data contain an unknown degree of bias. The NPIS relies principally on voluntary reporting of cases, although since 1980 by following up cases reported to the manufacturer or in newspapers the surveillance has been more complete. Official mortality statistics rely on the correct diagnosis of the cause of death which has been shown to be inaccurate in many instances of poisoning (Vale, Buckley & Meredith, 1984). If the number of deaths reported to the NPIS are compared to those reported by the OPCS and Registrar General of Scotland, the differences are small, e.g. 41 compared with 40 in 1982, 33 compared with 41 in 1983 and 32 compared with 30 in 1984. The degree of overlap remains unknown, requiring comparison of death certificates with NPIS records, and has not been possible within the scope of this study. In Eire, mortality statistics over the period 1967–1976 were obtained from a study combining official mortality and PCC statistics (Fitzgerald *et al.*, 1978), whilst after 1976, statistics were obtained solely from the PCC. There does not seem to be any great jump in the mortality trend shown in Figure 1 so perhaps differences between PCC and official mortality statistics are in fact small.

b. Other countries Mortality data from a survey into the incidence of paraquat poisoning amongst members of the EAPCC is shown in Table 4 together with information from other PCC's and literature. There are wide differences from country to country in the annual numbers of deaths due to paraquat per year, ranging from 1300 in Japan to 1 in Denmark and zero in Sweden. There are also wide variations in the number of fatalities per million population, e.g. 0.004 per million (USA) and 47.0 per million (Fiji). The mortality ratios range from 74% in one French study (Frelon *et al.*, 1983), 58% (Fiji) and 52% (Poland) to 0.6% (USA) suggesting that the proportion of suicides and accidental exposures are different in

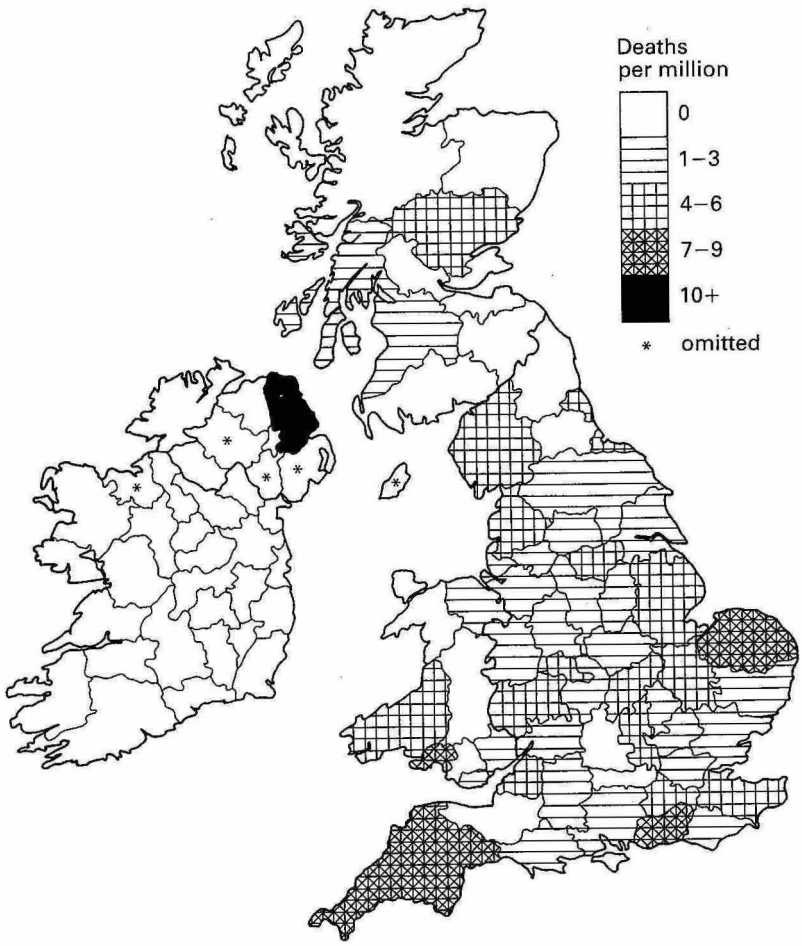

Figure 4 Deaths due to paraquat 1980–1985 (UK): Deaths per million population by county as reported to NPIS. (n = 173.)

different countries. Although the figures are not strictly compatible due to uncertainties with the populations covered, they do indicate that some countries have bigger problems with paraquat poisoning than others.

In France, paraquat poisoning has been monitored in detail by Poison Control Centres (Conso, 1979; Frelon, Merigot, Garnier *et al.*, 1983; Ethymiou, 1983). Paraquat was first marketed there in 1965, but fatalities were not recorded until 1973, rather later than in the UK. Accidental deaths declined in proportion to suicides over the period 1973 to 1977. All deaths resulted from ingestion. Ethymiou (1983) reported that although accidental and occupational poisoning represented 74% of all cases, suicidal poisoning was associated with the highest mortality, as were the more concentrated products. Over a three-year period only one child died. More cases were reported in rural areas. Hence the situation in France is very similar to the UK.

A series of reviews concerning poisoning cases in Malaysia (Amarasingham & Lee, 1969; Amarasingham & Hee, 1976 and Amarasingham & See unpublished data) found that paraquat has replaced arsenite as the most commonly consumed poison. From 1977 to 1981 paraquat was responsible for 31% of all poisoning cases, with 79% mortality. The incidence of males and females was similar and poisoning was predominantly due to its suicidal use by the poorer ethnic groups who presumably had greater access to the product. Accidental cases of poisoning occurred after the concentrated formulations were decanted locally into poorly labelled containers.

Table 4 Fatalities due to paraquat reported internationally (over the years 1980–1984)

Country	*Population (millions)*	*Deaths per annum (average)*	*Deaths per million population per annum*	*Cases per million population per annum*	*Mortality % (average)*	*Source*
UK	56.6	37.6	0.66	3.3	20	NPIS
England & Wales	49.6	30.3	0.61	—	—	OPCS
Scotland	5.2	8.2	1.6	—	—	Registrar General
Denmark	5.1	1.0	0.20	—	—	Copenhagen PCC
France	54.2	—	—	1.7	—	Wickstrøm*
		20.0	(0.36)	(0.5)	74	Frelan 1983
Germany (West)	61.6	1.3	0.02	—	—	Wickstrøm*
Greece	9.8	—	—	6.2	—	Athens
Eire	3.5	9.4	2.7	15.8	18	Dublin PCC
Netherlands	14.3	—	—	2.0	—	Wickstrøm*
Czechoslovakia	15.4	2.5	0.16	—	—	Wickstrøm*
Norway	4.1	0.25	0.06	—	—	Wickstrøm*
Poland	36.7	4.3	0.12	0.23	52	Wickstrøm*
Spain	37.9	—	—	0.9	—	Wickstrøm*
Sweden	8.3	—	—	0.07	—	Stockholm PCC
Switzerland	6.5	1.8	0.28	1.3	21	Wickstrøm*
Israel	4.1	1.5	0.37	—	—	Haifa PCC
Australia	15.4	—	—	0.6	—	Canberra PCC
Fiji	0.67	31.5	47.0	80.6	58	Groundar 1984
Japan	118.4	1300	11.0	—	—	Naito 1986
USA	232.0	1.0	0.004	0.7	0.6	AAPCC

* = Wickstrøm, E. personal communication

Population sources: Eurostat 'Basic Statistics of the Community' 1984
UK CSO 'Regional Trends' 1985

Prevention

A range of measures have been introduced or proposed for the prevention of paraquat poisoning.

1. Communication

Information concerning the toxicity of paraquat, correct usage and the dangers of inappropriate storage should be given to agricultural and domestic users. Product labelling is one way of communicating this information. The earliest product labels for paraquat gave no indication of its toxicity, but when the problem of poisoning became apparent appropriate changes were made and present day labels leave the user in no doubt about the need to handle the product with care. Labelling should be in an appropriate language with symbols carefully chosen to be meaningful to the user. For example in some parts of the world the snake is more meaningful as a hazard warning of poison than the skull and crossbones.

No matter how good the label, it cannot be assumed that the user will read it carefully. It is therefore important to use additional forms of communication; posters and booklets such as those produced by GIFAP (GIFAP 1983), appropriate audio visual aids and educational campaigns by the press and television regarding safe handling and storage. Media coverage of paraquat poisoning can have a detrimental effect; reports of individual cases, often sensationalised, may influence others to use paraquat as a means of suicide (Barraclough, Shephard & Jennings, 1977). Therefore restricting or controlling such publicity might help reduce the number of suicides using paraquat (Hayes, 1980).

2. Packaging

Restricting pack size is an obvious way to limit the dose likely to be ingested. Additionally the type of package can affect the accessibility of the product. The proposed Child Resistant Packaging Regulations will not require child resistant closures for paraquat containing products currently on sale in the UK since they will not apply to solids or products exclusively for use in agriculture [Child Resistant Packaging Regulations 1986 (Draft)]. It is unlikely that they would affect the incidence of serious poisoning in children since children do not ingest toxic amounts of

the domestic products or gain access to the commercial preparations in their original containers. Accidental poisoning with these products in adults and children normally occurs as a result of inappropriate decanting and labelling. Packaging changes are unlikely to deter the suicidal patient.

3. Formulation changes

Changes in the concentration of paraquat within a product will also limit the dose ingested. Thus the marketing of a 2.5% w/w granular formulation represents a reduction in hazard from the earlier 5% w/w formulation. It has been shown that the granular formulation is less of a hazard than the liquid concentration (Table 3) and it has been proposed in this respect that a diluted liquid concentrate, 10% w/v, should replace the 20% w/v product currently marketed.

Other formulation changes have involved the use of 'additives'. An unpleasant smelling 'stenching' agent was added to liquid formulations in 1975 and in 1981 a blue colour was added to liquid and solid paraquat products to serve as a warning.

In 1977 a centrally-acting emetic agent, codenamed PP796, was added to liquid formulations at a concentration of 0.05% w/v and to solid formulations at a concentration of 0.02% w/w. This concentration of emetic was calculated to cause vomiting if the minimum lethal dose was swallowed and in animal experiments such a concentration increased the lethal dose of paraquat by a factor of three to five (Rose, 1976). Recently (1985) the concentration of emetic in solid formulations has been doubled. Two authors have commented on the effectiveness of the emetic in reducing mortality in man. In France it was concluded that the emetic (identified in 14 cases, 11 of whom died) did not modify prognosis. In contrast preliminary findings of a study in the UK have found that there may be some reduction in mortality with emetic addition (A. P. Whitehead, personal communication). Emetic addition was not associated with any adverse effects (Denduyts-Whitehead, Hart & Volans, 1985). Even so the efficacy of the emetic at reducing mortality in man remains to be substantiated.

Another suggestion for prevention has been put forward as a result of the development of a novel formulation which forms a semi-solid mixture when small amounts of water are added, thus making it difficult to ingest large quantities (Naito & Yamashita, 1986).

4. Legislation

Legislation has restricted the availability of the commercial concentrate in many countries and in some countries a total ban has been applied (West Germany and Sweden). In the UK the Poisons Act of 1972 restricts the sale of concentrated formulations to 'persons engaged in the trade or business of agriculture, horticulture or forestry'. The sale of these concentrated products is further restricted by limiting the number of licenced dealers. In Eire, similar legislation was passed in 1968 and 1975. The effects of this legislation on the incidence of paraquat poisoning were studied by Fitzgerald *et al.* (1978) who found that there was a drop in the number of accidental poisonings, due to a decrease in the practice of decanting commercial products into household containers. There was no change in the number of suicides after this legislation was passed. Legislation may have the effect of increasing other forms of suicidal poisoning. It was following a ban of arsenite as a weedkiller in Malaysia in 1976 that paraquat poisoning became such a problem (Amarasingham & See, unpublished data). Those countries where paraquat is banned can be seen from Table 2 to have a very low incidence of paraquat poisoning. However such a severe course of action may not be appropriate for all countries and must take into account the agricultural importance of paraquat in that country.

Asked whether measures taken against paraquat poisoning had been effective, members of the European Association of Poison Control Centres (EAPCC) concluded that the addition of an emetic or staining agent had not had the desired effect and that strict regulations on the sale of the liquid concentrate did not seem to be wholly effective (Wickstrøm, personal communication).

Discussion

Comparisons of the incidence and severity of paraquat poisoning between different countries are severely limited by the lack of standardised methods of official data collection and recording. Nevertheless it is apparent that paraquat remains an important cause of mortality worldwide and there is little evidence that paraquat poisoning is decreasing in frequency.

There are differences in the incidence of paraquat poisoning amongst the countries studied. There are also regional differences within the UK, Northern Ireland and Scotland have higher incidences than England and Wales, and paraquat poisoning in Eire has always had a higher incidence than in the UK. In some countries paraquat has not so far presented a serious problem in spite of its widespread usage—for example, USA and Australia. In contrast Japan and a number of other countries, notably Fiji, are currently facing epidemics of paraquat poisoning far more severe than those seen in Europe.

Mortality from paraquat poisoning is closely related to suicidal intent; thus in the USA (mortality 0.6%) 88% of cases were accidental whilst in Fiji (mortality 58%), 66% had suicidal intent. Additionally the predominance of males amongst fatalities correlates well

with the known epidemiology of suicides (Weissman, 1974).

The increase in suicidal use of paraquat in the UK over the period 1966–1975, accounts for the rise in fatalities (Figure 3). Why there should have been this increase in so many countries is unknown. In the UK there was no proportionate increase in sales of the commercial product over the period when the rapid increase in fatalities occurred (T. B. Hart, personal communication). However the availability of the liquid concentrate remains an important factor. The wide range of occupations recorded amongst fatalities may mean that legislation restricting the availability of paraquat is not sufficient. Substitution and public awareness are additional factors which may influence the use of a particular product for suicide (Low *et al.*, 1981). Substitution has been shown to have had an effect in Malaysia where paraquat replaced arsenite poisoning but the influence of substitution in the UK is not known. Public awareness, increased by media reporting may be an important factor but remains difficult to investigate.

In many countries serious accidental and occupational poisoning and poisoning in children is rare. The nature of paraquat poisoning is largely suicidal and it is unlikely that current preventative measures will influence the number of deaths occurring each year. Few preventative measures have been monitored in such a way as to demonstrate their effectiveness.

On the basis of our experience in the UK, we believe that Poison Control Centres (PCCs) have an important role in monitoring the incidence and severity of poisoning and providing epidemiological data. PCCs are well placed then to develop schemes to evaluate preventative measures. Care must be taken when making direct comparisons between different PCCs because of the different populations covered and differences in the methods used to assess cases. There is currently much interest in the suggestion that PCCs should agree to standardise some aspects of data collection. We would tentatively suggest that since paraquat poisoning in Europe is widespread and involves relatively small numbers of a discrete type of poisoning it would form a useful model for international collaboration between PCCs.

The authors acknowledge the help of colleagues in the National Poisons Information Service and other Poison Control Centres and, in particular, the information provided by Dr E. Wickstrøm and Professor A. N. J. van Heijst on behalf of the European Association of Poison Control Centres. We should also like to thank John Gelder for his help with the illustrations.

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Mechanism of Paraquat Toxicity in Lung and its Relevance to Treatment

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1 The symptoms of paraquat poisoning depend largely on the amount of compound consumed, although in many cases the most characteristic feature of poisoning is lung damage, causing severe anoxia which leads to death.
2 Studies in experimental animals have demonstrated that paraquat produces an acute damaging phase in the lung, followed by a reparative phase dominated by an extensive fibrosis. The latter is a major contributor to the lung lesion that causes anoxia. The specific toxicity in the lung can be explained in part by the selective accumulation of paraquat into this organ in comparison with other tissues. The accumulation is energy-dependent and probably specific to certain lung cells.
3 It is now known that paraquat is accumulated into the lung by a recently described diamine transport process located in the alveolar epithelial cells and the Clara cells of the airways. When accumulated, paraquat undergoes a NADPH-dependent one-electron reduction to form its free radical which almost instantly reacts with molecular oxygen to reform the cation and concomitantly produce superoxide anion. This species of oxygen radical can contribute to the formation of more toxic species of radical which may directly damage vital cellular constituents.
4 Paraquat has been shown to stimulate rapidly the pentose phosphate pathway and inhibit the synthesis of fatty acids in the lung in a dose-dependent manner. In addition there is a rapid increase in the pulmonary levels of mixed disulphides and the eventual reduction of NADPH levels in the lung.
5 These results are consistent with the suggestion that paraquat causes a rapid and pronounced oxidation of NADPH which initiates compensatory biochemical responses in the lung.
6 With toxic levels of paraquat the compensatory biochemical processes are insufficient to maintain levels of NADPH consistent with cell viability. Thus, cell death may result from NADPH depletion, or the loss of this vital co-factor may render the lung more susceptible to free-radical attack and thereby peroxidation of vital cellular constituents.

Introduction

The structure of the herbicide paraquat (1,1′-dimethyl-4,4′-bipyridilium) was first described by Weidel & Rosso (1882). In 1933, its redox properties were discovered by Michaelis & Hill and it has since been used as a redox indicator known by the trivial name methyl viologen. In the 1950s, its herbicidal properties were discovered by Imperial Chemical Industries PLC and its is now marketed as a contact herbicide in over 130 countries throughout the world.

The safety of paraquat in its correct use is well documented (T. B. Hart, unpublished work). However, there have been numerous human fatalities from acute paraquat poisoning. The vast majority of these have resulted from the intentional ingestion of the concentrated commercial product for suicidal purpose. The symptoms of poisoning depend on the amount consumed. Those patients who consume large amounts of paraquat die within a few days of its ingestion, whereas others (who consume less) die many days or weeks later. With these later deaths the cause is usually pulmonary damage characterized by pulmonary fibrosis.

It is the purpose of this review to describe what is presently understood of the mechanism of paraquat toxicity in the lung and in the process provide a framework for an appreciation of the various approaches which have been, or could be, undertaken to improve the treatment of paraquat poisoning.

Morphological changes in the lung

There are numerous reports that describe the morphological changes in the human lung caused by paraquat. However, for a proper appreciation of the

development of the lung lesion, studies in experimental animals are necessary. The rat is probably the most extensively studied species in terms of the response of its lung to paraquat toxicity. In general, there are two distinct phases to the development of the pulmonary lesion. First, is a destructive phase in which the alveolar epithelium of the lung (type I and type II epithelial cells) are destroyed (Smith & Heath, 1974, 1976; Smith *et al.*, 1974a). If the destruction of the alveolar epithelium is extensive, an alveolitis develops, associated with pulmonary oedema and the infiltration of neutrophil polymorphs into the lung. In the case of rats, this acute alveolitis may be severe enough to cause death. The second phase of the lung lesion can be regarded as a consequence of the acute damage to the alveolar epithelium and resulting alveolitis (Smith & Heath, 1976). In this phase, an extensive intra-alveolar and interalveolar fibrosis develops which may be so widespread and severe as to destroy completely the normal alveolar architecture. With the obliteration of the alveolar membranes and their replacement with fibrous tissue, the opportunity for effective gaseous exchange is reduced and this may be severe enough to cause death from anoxia.

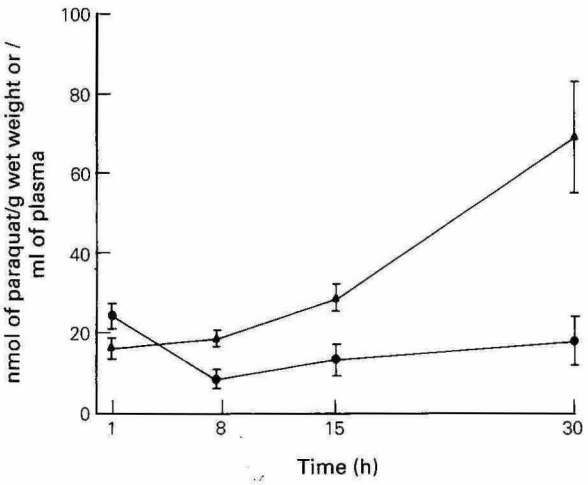

Figure 1 Relation between lung (▲) and plasma (•) concentrations of paraquat following an oral dose of paraquat. Level of paraquat in the lung and plasma of rats given 680 μmol of paraquat/kg body weight orally. Points on the graph represent mean ± SEM. At least five rats per time point [L. L. Smith, A. F. Wright, I. Wyatt & M. S. Rose (1974b) *Br. Med. J.*, **iv**, 569–571]

Uptake of paraquat from the gastrointestinal tract

When paraquat is administered orally to rats, the concentration of paraquat in the plasma is determined largely by the amount of paraquat present in the small intestine (Smith *et al.*, 1974b). Also, when dogs were given paraquat orally and drugs were administered to decrease stomach emptying time, the concentration of paraquat in the blood was decreased (Bennett *et al.*,1976). However, when dogs were given paraquat and drugs to increase stomach emptying time, the plasma paraquat concentration was increased compared with control animals (Bennett *et al.*, 1976).

These data from both rats and dogs indicate that the absorption of paraquat largely occurs from the gastrointestinal tract somewhere beyond the stomach. It is assumed that this is the case in humans, although there does not appear to be any good evidence as to the site of paraquat's absorption.

It was found after the oral administration of paraquat to rats that the plasma paraquat concentration remained relatively constant for 30 h, during which time the concentration in the lung rose progressively to several times that in the plasma (Figure 1). In no other organ studied was this time-dependent accumulation of paraquat detected (Rose *et al.*, 1976). However, it should be noted that the kidney, which is the organ responsible for the excretion of paraquat from the plasma, also has high concentrations in comparison with other organs. Thus the selective accumulation of paraquat into the lung and its high concentrations in the kidney provides a plausible explanation why these organs are those selectively damaged by paraquat following oral dosing (Smith *et al.* 1974b; Rose *et al.*, 1976).

Accumulation of paraquat into the lung

Using lung slices, Rose *et al.* (1974) first described the time-dependent accumulation of paraquat into lung tissue. This process was found to be energy-dependent in so far as it could be inhibited by the addition of the metabolic inhibitors cyanide and iodoacetate to the incubation medium (Rose *et al.*, 1974). The accumulation of paraquat into the rat lung obeys saturation kinetics and various species of animal have the ability to accumulate paraquat (Rose *et al.*, 1976). As can be seen in Table 1, the apparent kinetic constants for the rat and human lung are similar, suggesting that the

Table 1 Apparent kinetic constants for the accumulation of paraquat into the lung of several animal species

Species	K_m (μM)	V_{max} ($nmol\,h^{-1}\,g^{-1}$)
Rat	70	300
Mouse	68	556
Syrian hamster	77	452
Guinea pig	96	49
Rabbit	0.05	20
Man	40	300

rat lung can be used as an acceptable model for the study of the accumulation of paraquat into human lung.

The discovery of an energy-dependent accumulation of paraquat into lung tissue lead to the search for chemicals which might inhibit this process (Lock *et al.*, 1976). Also, it was reasoned that the uptake system present in the lung was functioning to accumulate an endogenous compound(s) and that paraquat was mistakenly accumulated by this process (Smith, 1982). A number of endogenous diamine and polyamine compounds were found to reduce the accumulation of paraquat into the lung (Smith, 1982) and were themselves accumulated by the uptake process responsible for the accumulation of paraquat (Smith, 1982; Smith *et al.*, 1982).

The most likely reason for the accumulation of paraquat by the lung is its structural similarity to the diamine and polyamine compounds which are, at least in parts, the endogenous substrates for the system. The structural requirements for compounds to be accumulated into the lung have been partially characterized and it appears that the distance between the quaternary nitrogen atoms of paraquat is critical in allowing the molecules to be mistakenly accumulated by the diamine and polyamine uptake system (Smith, 1982; Gordonsmith, 1983).

There is little direct evidence describing the cellular compartment into which paraquat and the polyamines are accumulated. However, Waddel & Marlowe (1980) showed that in mice, intravenously dosed with labelled paraquat, the label present in the lung had a distribution consistent with that of alveolar type II cells. Studies from this laboratory (both *in vitro* and *in vivo*) have shown that the distribution of ^{14}C-labelled paraquat and the ^{14}C-labelled polyamines, putrescine and spermidine, was confined to the alveolar epithelial cells (type I and II) while the polyamines were also present in the Clara cells. Thus it appears that the alveolar epithelial cells which are those damaged by paraquat are at least in part a site of accumulation.

Mechanism of toxicity

Gage (1968) first reported that under anaerobic conditions the paraquat cation could be reduced by NADPH-dependent microsomal flavoprotein reductase to form its reduced radical. This in turn reacts avidly with molecular oxygen (Farrington *et al.*, 1973) to reform the paraquat cation and concomitantly produce superoxide anion. Provided that there is a continuous supply of electrons to paraquat and oxygen is present, paraquat will continue to cycle from its oxidized to reduced form with the resultant production of superoxide anion. This redox cycling of paraquat has been shown to occur in microsomal preparations from liver, lung and kidney (Baldwin *et al.*, 1975).

It is accepted generally that the redox cycling of paraquat is the primary reaction in its mechanism of toxicity. However, the biochemical consequences of this reaction which leads to cell death are still unclear. There have been numerous reports of the ability of paraquat to cause lipid peroxidation based on the original hypothesis of Bus *et al.* (1974, 1975, 1976). However, there is little direct evidence which demonstrates that lipid peroxidation occurs in the lung of animals treated with paraquat before there is morphological evidence of cell damage. While this may reflect the difficulty of detecting a small but critical increase in lipid peroxidation within the target cells of the lung, it is also possible that lipid peroxidation *per se* is not the cause of cell damage but is in fact a consequence of it. An alternative suggestion is that with the accumulation of paraquat to high concentrations within a small proportion of the lung cells, redox cycling occurs to such an extent that NADPH levels within these cells are reduced so that the cells essential physiological and biochemical functions can no longer be carried out. Fisher *et al.* (1975) first suggested that the redox potential of cells may be altered by the cycling of paraquat. Witschi *et al.* (1977) then demonstrated that the NADPH/NADP$^+$ ratio in the lungs of rats intravenously dosed with paraquat was decreased suggesting the oxidation of the reduced nucleotide. In further studies, Keeling & Smith (1982) demonstrated that the shift in the NADPH/NADP$^+$ ratio was a result of a loss of NADPH from the lung. The NADPH is also consumed in an attempt by the lung to detoxify hydrogen peroxide that is formed via the glutathione peroxidase and reductase enzyme systems. Thus, NADPH is consumed in the formation of hydrogen peroxide and is further consumed in its detoxification. Figure 2 attempts to summarize the possible mechanisms of paraquat toxicity in the lung.

Relevance of mechanism of toxicity to treatment regimens

From an understanding of the mechanism of paraquat toxicity it is apparent that there are several approaches which can be adopted to reduce its acute toxicity. Some of these are summarized below: (1) prevent the absorption of paraquat from the gastrointestinal tract into the plasma; (2) prevent the accumulation of paraquat into the lung; (3) prevent the redox cycling of paraquat in the lung; (4) increase the elimination of paraquat from the lung; (5) reduce the acute alveolitis which develops; (6) reduce the pulmonary fibrosis.

The use of adsorbants to prevent the absorption of paraquat from the gastrointestinal tract into the

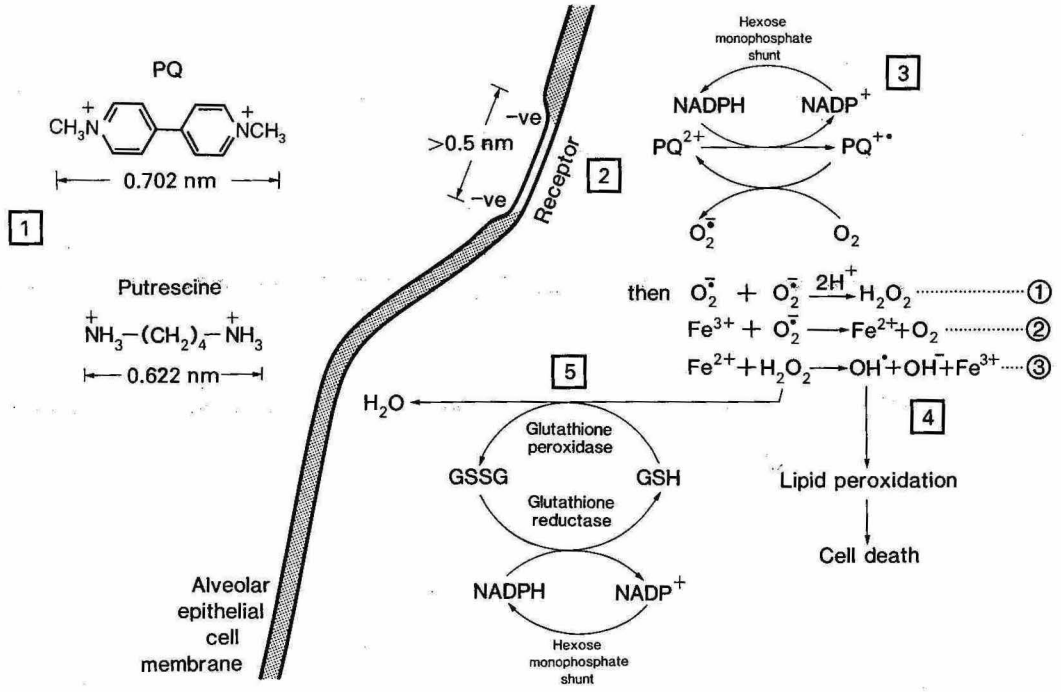

Figure 2 Mechanism of toxicity of paraquat. Schematic representation of mechanism of toxicity of paraquat. 1 = structure of paraquat and putrescine showing geometric standards of the distance between N atoms; 2 = putative accumulation receptor with a minimum separation of charge of approximately 0.5 nm (optimal distance unknown); 3 = redox cycling of paraquat utilizing NADPH; 4 = formation of $OH^{\bullet}$ radical leading to lipid peroxidation; 5 = detoxification of H_2O_2 via glutathione reductase/peroxidase couple, utilizing NADPH

plasma has been reviewed elsewhere (T. J. Meredith & J. A. Vale, unpublished work). Nevertheless, it is worth highlighting one important feature of the use of adsorbants. When these were recognized as a potential treatment for paraquat poisoning it was possible to demonstrate that rats given lethal doses of paraquat could be protected when Fuller's Earth or bentonite was given 4 or even 10 h after the oral administration of paraquat. The kinetics of the absorption of paraquat from the gastrointestinal tract and its subsequent accumulation into the lung described in Figure 1 provides a rational basis for this protection. The concentration of paraquat in the plasma remains constant for approximately 30 h, whereas the lung accumulates high concentration during this time (Figure 1). If the plasma concentration of paraquat is reduced by preventing the absorption of paraquat from the gastrointestinal tract into the plasma then the lung does not accumulate lethal concentrations (Smith *et al.*, 1974b). The absorption of paraquat from the gastrointestinal tract into the bloodstream of humans who have ingested paraquat (Figure 3) is quite different to that seen in the rat. Paraquat is absorbed rapidly leading to peak plasma concentrations within a few hours of ingestion. Thereafter, the concentration of paraquat in the plasma falls rapidly to much lower concentrations than described in Figure 1 for the rat. Thus, in man, if adsorbants are to be effective in preventing paraquat moving into the bloodstream and consequently the lung, they must be administered within a few hours of ingesting paraquat. This is quite different to the original conclusion based on studies in the rat which suggested that adsorbants should be given for at least the first 24 h after paraquat had been ingested.

The rapid absorption of paraquat into the blood of humans is also relevant to the second approach to treatment, which is the removal of paraquat from the plasma by either haemoperfusion or haemodialysis. These techniques are likely to be most effective when they are applied early and certainly before the concentration of paraquat in the plasma has fallen to very low levels. Thus, given the shape of the paraquat plasma curve in man, haemoperfusion must be introduced within the first 10 h if it is to be effective in reducing the plasma paraquat concentration and thereby prevent its accumulation into the lung.

Although the redox cycling of paraquat is critical to its mechanism of toxicity there are no reports to suggest that this process can be inhibited *in vivo*.

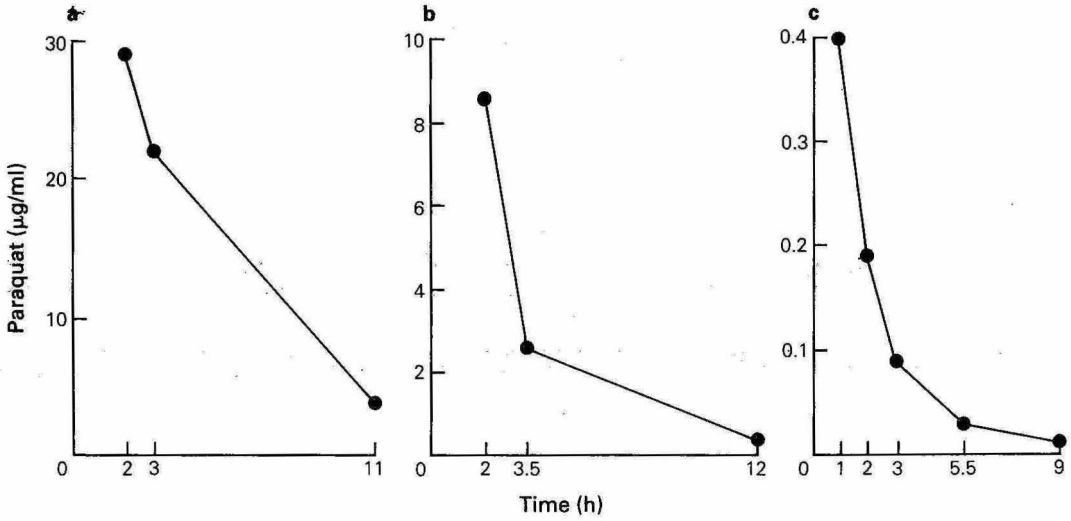

Figure 3 Plasma paraquat concentrations in poisoning cases at early time points. Level of paraquat in the plasma of three patients who had ingested various quantities of paraquat [half a cupful of Gramoxone approximates to 20 g of paraquat ion; one sachet approximates to 1.25 g of paraquat ion (PQ^{++})]. **a**, ~ 20 g of PQ^{++} as liquid, died; **b**, ~ 10 g of PQ^{++} as granular formulation, died; **c**, ~ 3 g of PQ^{++} as granular formulation, survivor

Factors affecting the elimination of paraquat from the lung have been investigated (Smith *et al.*, 1981). However, these studies were carried out *in vitro* and with the exception of the effect of cyclophosphamide on the rate of elimination of paraquat from the lung *in vivo* (L. L. Smith & S. C. Watson, unpublished work), little progress has been made with this approach.

Attempts have been made to reduce the acute alveolitis caused by paraquat as well as the subsequent fibrosis. The basis for the claimed effectiveness of cyclophosphamide and dexamethasone in treating human cases of paraquat poisoning (Addo *et al.*, 1984) is the ability of cyclophosphamide to reduce the number of circulating neutrophil polymorphs in the blood and thereby reduce the number that infiltrate the damaged lung. By reducing the number of neutrophils in the lung it is thought that the extent and severity of the fibrosis will be reduced. However, whether this proves to be an effective treatment for paraquat poisoning remains to be seen.

Conclusion

In conclusion, the mechanism of paraquat toxicity involves its absorption from the gastrointestinal tract into the blood, followed by transport to the lung and accumulation into specific alveolar epithelial cell types. Once accumulated, paraquat redox cycles consuming the reducing equivalents of the cell and generating superoxide anion. Either the loss of NADPH and resulting oxidative stress or lipid peroxidation resulting from the generation of reactive oxygen radicals, or a combination of both processes, results in cell death. This initiates an acute alveolitis characterized by oedema and infiltration of neutrophil polymorphs. If this alveolitis is severe enough a resolving fibrosis develops which obliterates the normal alveolar architecture preventing gaseous exchange and causing death from anoxia. Thus an understanding of the mechanism of toxicity of paraquat has provided a basis for the development of rational and effective treatments for cases of human poisoning.

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Paraquat Poisoning: The Rationale for Current Treatment Regimes

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1 The critical events leading to death from the ingestion of paraquat are absorption from the gastrointestinal tract, active accumulation in the lung almost certainly preceded by acute renal failure and redox cycling in the lung which initiates certain, as yet unidentified, biochemical events leading to cell death with subsequent destruction of the lung and death from anoxia.
2 Present evidence suggests that absorption of paraquat is rapid and the use of adsorbents more than 6 hours after ingestion is likely to be ineffective. Further work is needed to characterize the mechanism of absorption and to identify an innocuous chemical which could be added to formulations of paraquat to inhibit absorption; this approach may be the best solution to the problem of paraquat poisoning.
3 Steps to actively remove paraquat from the systemic circulation will probably only succeed in a small number of patients taking moderate doses and developing early renal failure. The 'window' for such treatment may be as narrow as 6–18 h after ingestion. This 'window' would also operate for chemicals designed to inhibit the pulmonary uptake of paraquat.
4 The biochemical events leading to paraquat-induced cell death are not sufficiently defined to permit the design of treatments to prevent or reverse these processes.

Introduction

Paraquat (1,1′-dimethyl-4,4′-dipyridyl) is a widely used contact herbicide which is safe during normal use but causes severe, often fatal, toxic effects following ingestion of concentrated solutions. The cause of death depends upon the amount consumed but is usually either multiple organ failure or late-developing pulmonary fibrosis (which is almost invariably preceded by the development of renal failure).

Paraquat appears to be rapidly, but incompletely absorbed from the gastrointestinal tract.[1] Once in the systemic circulation it accumulates slowly in the lungs, a major target organ for toxicity, by an energy-dependent process.[2] Paraquat accumulates rapidly in kidneys and is almost quantitatively eliminated from the body in urine.[3] The chemical is not metabolized to a significant extent. Early onset of renal failure greatly reduces the total body clearance of paraquat and has a profound effect on its distribution.[3]

In dealing with paraquat poisoning, as with any other chemical, treatment has concentrated on limiting absorption from the gastrointestinal tract and enhancing elimination from the systemic circulation. With a better understanding of the mechanisms of toxicity, procedures aimed at preventing accumulation in or promoting removal from target cells have been sought. Alternatively, attempts have been made to inhibit or reverse the biochemical events associated with cell death.

This paper considers the limited experimental and theoretical data which support treatments currently used in paraquat poisoning

Absorption of Paraquat

The early literature on paraquat reported a slow and poor (< 5%) absorption from the gastrointestinal tract in animals and in man. However, careful studies in conscious dogs[1] revealed a rapid but incomplete absorption. In the same studies it was shown that the absorption of paraquat was more rapid than another bipyridyl herbicide, diquat.

Studies with tracer doses of radio-labelled paraquat were conducted in dogs. Following intravenous dosing, plasma concentrations declined rapidly (Figure 1) and almost 90% of the injected dose was excreted in the urine in 6 h (Figure 2). Following an

oral dose, peak plasma concentrations were observed at 75–90 min (Figure 1) and almost 40% was absorbed in 6 h as judged by the amount excreted in the urine (Figure 2). Thus it appeared that there was a 'window' for paraquat absorption in the dog intestine. The precise site of absorption has not been identified but pretreatment of dogs with drugs which change the speed of gastric emptying confirmed that it is beyond the stomach. The nature of the process of absorption has not been elucidated but it is unlikely that simple diffusion would explain the rapid absorption of this highly charged chemical.

The apparent 'window' for absorption, the difference between paraquat and diquat and some evidence for saturation of the process suggest active transport. However, studies both *in vivo* and with isolated preparations of dog intestine *in vitro* have failed to find an active transport for paraquat.

Information on paraquat absorption in man is sparse. Data published from this Department[4] and results given at this symposium[5,6] show plasma concentrations to be falling in the early hours following ingestion. This suggests that in the poisoned patient paraquat absorption may be rapid, but incomplete, as in the dog with peak levels at 2 h. If this is true then heroic procedures to clear paraquat from the gastrointestinal tract 4–6 h or more following ingestion may be removing that proportion of the dose which will not be absorbed to a great extent. More information is needed on the extent and rate of absorption of paraquat in the poisoned patient.

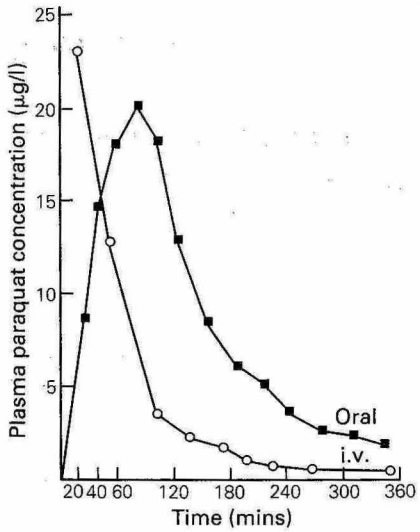

Figure 1 Plasma levels of paraquat in the dog after intravenous (393 μg) or oral (1030 μg) dosing. (Reproduced from Davies *et al.*[10])

Distribution and elimination of paraquat

Pharmacokinetic studies in dogs using tracer doses of radio-labelled paraquat have identified the major route of elimination. These studies also revealed the effect of paraquat-induced renal failure on the distribution of the chemical in the body.[3]

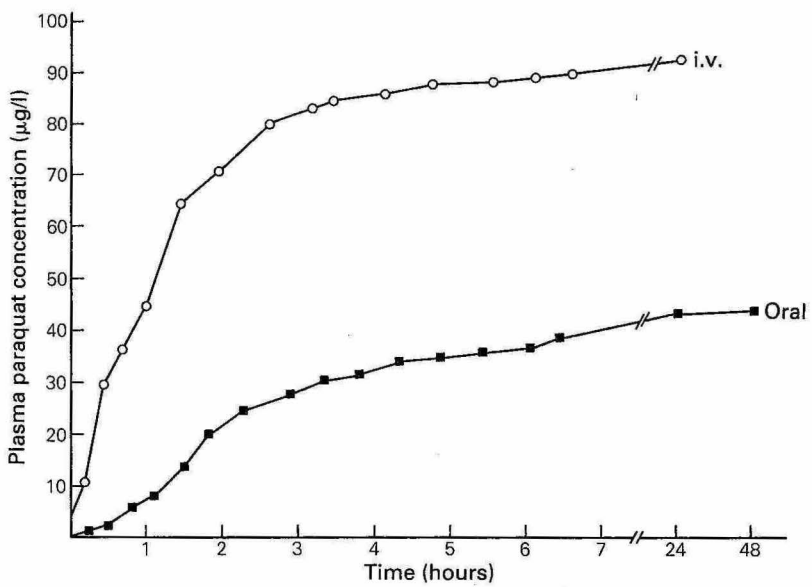

Figure 2 Excretion of paraquat in urine of dogs following an intravenous (393 μg) or oral (1030 μg) dose

Paraquat administered into the systemic circulation is rapidly and quantitatively eliminated by the kidneys. The renal clearance of non-toxic doses of paraquat exceeds the glomerular filtration rate in dog and man. In dogs the renal clearance of paraquat is reduced by the co-administration of another strong base, N^1-methylnicotinamide (NMN). It is assumed that NMN competes with paraquat for the strong base secretory mechanism in renal tubular cells (Table 1). A high dose of paraquat (20 mg/kg) given intravenously to dogs produces a rapid and profound decline in renal function with the renal clearance of paraquat and creatinine falling to a few ml/min within 2–3 h.[3]

The distribution of paraquat in the body is best described by a three-compartment open model with input to and elimination from the central compartment (Figure 3). Simulation of concentrations of paraquat in peripheral compartments showed that early onset of renal failure produced a fivefold increase in levels of paraquat (Figure 3).

Paraquat is accumulated in the target cells in the lung by an energy-dependent process.[2] Preliminary data (unpublished, Hawksworth, Bennett & Davies) using ^{11}C-labelled paraquat suggested that the uptake into lung in dog is slow and approximates to the time course of paraquat appearance in compartment 3 (Figure 3). Thus final concentrations of the toxin in lung may therefore be greatly influenced by the time of onset and degree of renal failure.

These data suggest that in a very small number of patients who have taken moderate doses of paraquat and develop early renal failure there may be a period of 12–18 h when removal of the chemical from the blood may prevent the accumulation of toxic levels in the lung. In those circumstances the total amount of paraquat removed is not important. The aim should be to reduce the blood level of the chemical and keep it down until renal function returns or there is insufficient left in the body to redistribute and damage the lung. It may be necessary to continue removing paraquat for several days.

Table 1 Reduction of the renal clearance of paraquat in dogs by co-administration of N-methylnicotanamide (NMN)

Animal	*Treatment*	*Clearance (ml/min)*	
		Paraquat	*Creatinine*
B	None	135	57
	NMN	52	50
F	None	152	52
	NMN	64	55
G	None	66	35
	NMN	33	35

Intravenous paraquat (30 mg/kg) followed by (90 min later) 0.2 mg/kg/min NMN

Methods of removal are discussed in other papers[5,7] but perhaps it is time to look again at peritoneal dialysis. The advantages are speed of institution and ease of use. The disadvantages include relatively poor clearances. The use of new osmotic agents may improve clearance. Preliminary studies in dogs using a glucose polymer showed promising results for paraquat clearance by peritoneal dialysis (Davies, unpublished results).

The narrow time frame for active removal of paraquat also applies to attempts to prevent accumulation of the chemical in the lung. Much is known about the paraquat uptake process in the lung[6] and a number of uptake inhibitors have been found. However, the ideal cheap, clinically useful, uptake inhibitor which can be formulated with paraquat has not been identified.

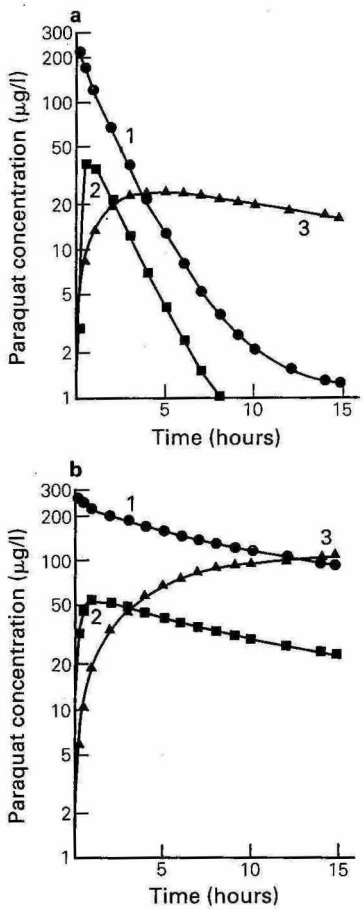

Figure 3 Computer simulation of paraquat kinetics in dog 1. 1 represents the central compartment, which includes the plasma, and 2 and 3 are the rapidly and slowly equilibrating peripheral compartments, respectively. (A) k_{10} = 0.0115 min^{-1}: (B) k_{10} = 0.0006 min^{-1}. (Reproduced from Hawksworth *et al.*[3])

Mechanism of toxicity of paraquat

Paraquat is readily reduced by microsomal enzymes from lung to a radical ion.[8–10] In the presence of oxygen the radical ion is oxidized with the formation of superoxide which may damage cells directly or through the generation of other active oxygen species. The involvement of the redox cycling of paraquat in its mechanism of toxicity is not in doubt. However, the biochemical events leading to cell death have not been identified.[6] Inhibition of the reduction of paraquat *in vivo* has not been achieved and in the absence of information on the subsequent biochemical events, treatments based on inhibition or reversing these processes have not been developed.

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Paraquat poisoning: clinical features and immediate general management

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1 In contrast to 10–15 years ago most cases of paraquat poisoning are now due to deliberate self-poisoning with parasuicidal or suicidal intent rather than to accidental ingestion. Less commonly, poisoning may follow careless handling of paraquat during occupational use. Although paraquat can be absorbed through the skin if improperly handled, poisoning usually follows ingestion and has rarely been reported after subcutaneous, intravenous or intraperitoneal injection.

2 Clinically, three degrees of intoxication may be distinguished. (a) Mild poisoning occurs after the ingestion or injection of less than 20 mg of paraquat ion/kg body weight. In these cases patients are either asymptomatic or symptoms are confined to the gastrointestinal system. All patients recover fully. (b) Moderate to severe poisoning usually follows the ingestion (rarely injection) of 20–40 mg of paraquat ion/kg body weight. Non-specific symptoms of ill health together with local gastrointestinal symptoms precede the development of renal failure (which may recover spontaneously) and pulmonary fibrosis which may not be manifest for days or weeks. Death occurs in the majority of cases but is usually delayed for 2–3 weeks. (c) Acute fulminant poisoning follows the ingestion of substantial quantities of paraquat (> 40 mg of paraquat ion/kg body weight). In addition to local symptoms, multiple organ (cardiac, respiratory, hepatic, renal, adrenal, pancreatic, neurological) failure occurs. Death may supervene within hours and is never delayed for more than a few days.

3 Initial general management has four priorities. Firstly, fluid loss should be replaced; secondly, the prognosis should be determined by measurement of the plasma paraquat concentration; thirdly, symptoms due to ulceration of the oropharynx must be relieved; fourthly, supportive care for patients and relatives must be provided.

4 Experience suggests that management of the terminally ill patient with acute fulminant poisoning is a far greater clinical challenge to medical and nursing expertise than simply the employment of methods to prevent absorption or increase elimination of paraquat.

Introduction

Paraquat is a widely used herbicide that is marketed either in granular form (25–80 g/kg, e.g. Weedol, Pathclear, Speedway) or as a water-soluble concentrate (100–200 g/l, e.g. Gramoxone, Dextrone). In the UK, the concentrated preparations can, under poisons law [Poisons Act, 1972; The Poisons Rules 1982, The Poisons List Order, 1982 (as amended)], only be supplied to bona fide agriculturalists and horticulturalists.

Local toxicity: skin, nails, eyes, nose

Paraquat, especially in concentrated formulations, has a strong irritant action on various types of epithelia. Thus, it will cause erythema, blistering, irritation and ulceration of the skin and eczematous dermatitis has been reported (Botella *et al.*, 1985). Paraquat diluted as recommended for spraying is unlikely to irritate the skin unless clothing soaked with spray is worn for prolonged periods.

Concentrated solutions of paraquat may also cause localized discoloration or a transverse band of white discoloration affecting the nail plate, though the latter damage may not become apparent for several weeks. Transverse ridging and furrowing of the nail progressing to gross irregular deformity of the nail plate and loss of nail may also occur (Samman & Johnston, 1969; Hearn & Keir, 1971; Botella *et al.*, 1985). Normal nail growth follows without delay once exposure has ceased.

Severe inflammation of the cornea and conjunctiva may follow the accidental splashing of paraquat concentrate into the eyes. The inflammation develops gradually, reaching a maximum after 12–24 h, and

may lead to ulceration of the conjunctiva and cornea (Joyce, 1969) with the risk of secondary infection. Although healing may be slow, recovery is usually, though not always, complete (Cant & Lewis, 1968a,b; Deveckova *et al.*, 1980). Serious ophthalmic complications may ensue if the casualty does not recognize the potential seriousness of exposure. In these circumstances, the patient may present with marked reduction in visual acuity due either to corneal oedema or a corneal opacity (Swan, 1968; Joyce, 1969). Lachrymal duct stenosis has also been described (Karai *et al.*, 1981).

Inhalation of fine spray droplets through careless use can cause epistaxis and sore throat.

Systemic toxicity

In contrast to 10–15 years ago, most cases of paraquat poisoning are now due to deliberate self-poisoning with parasuicidal or suicidal intent rather than to accidental ingestion, as may occur if the herbicide is decanted into a wine or soft-drink bottle. Occasionally, food and drink may be adulterated with paraquat with intent to harm (Watts, 1985) or murder (Teare & Brown, 1976). Less commonly, poisoning may follow careless handling of paraquat during occupational use. Although paraquat can be absorbed through the skin if improperly handled, poisoning more usually follows ingestion or, rarely, injection of the herbicide. There is no conclusive evidence that systemic toxicity has ever followed inhalational exposure to paraquat.

Systemic toxicity after percutaneous absorption

Normally, the surface epithelium of the skin is an excellent barrier to paraquat (Walker *et al.*, 1983), but prolonged skin contact with the herbicide may not only cause a chemical burn with blistering and ulceration but also serious and even fatal poisoning. Systemic toxicity is more likely to result if the paraquat solution is concentrated, exposure is prolonged and the skin traumatized (Newhouse *et al.*, 1978). These conditions may be encountered as the result of the following. (1) *Poor occupational practice*. The use of leaking spray apparatus (Jaros, 1978; Levin *et al.*, 1979; Withers *et al.*, 1979; Wohlfart, 1982; Athanaselis *et al.*, 1983), the non-use of protective clothing (Newhouse *et al.*, 1978), prolonged wearing of contaminated clothing and failure to wash contaminated skin (Athanaselis *et al.*, 1983), may all result in serious poisoning). (2) *Carelessness*. A farmer from Belize fell off his bicycle with a bottle of paraquat in his pocket. He did not remove his trousers for several hours and ultimately died 12 days later (Waight, 1979). In another incident, an adult cleaned his perineum with paraquat by mistake. He developed renal and respiratory failure and required mechanical ventilation for 5 days but eventually recovered (Tungsanga *et al.*, 1983). (3) *A mistaken belief in the therapeutic efficacy of paraquat.* Paraquat has occasionally and inappropriately been used as a treatment for lice and scabies (Ongom, 1974; Binns, 1978; Wohlfart, 1982), sometimes with serious consequences. (4) *Accident*. After spillage of paraquat, children may be contaminated, their skin not washed, the danger to their health not recognized and severe complications ensue (Okonek *et al.*, 1983).

Systemic toxicity after injection

Systemic toxicity has followed the subcutaneous (Almog & Tal, 1967), intraperitoneal and intravenous (Harley *et al.*, 1977; Hendy *et al.*, 1984) injection of paraquat.

Clinical features of paraquat poisoning

This review is based on the personal clinical experience of the authors obtained through the treatment of approximately 150 patients. In addition, a comprehensive review of the literature has been undertaken, but, for the purpose of brevity, only references to uncommon complications have been cited. Three degrees of intoxication may usefully be distinguished.

Group 1

Mild poisoning follows the ingestion or injection of < 20 mg of paraquat ion/kg body weight [i.e. < 1 sachet of 2.5% (w/v) Weedol]. Patients are asymptomatic or develop vomiting and diarrhoea. Full recovery occurs but there may be a transient fall in the gas transfer factor (TLCO) and vital capacity.

Group 2

Moderate to severe poisoning follows the ingestion or injection of 20–40 mg of paraquat ion/kg body weight (i.e. > 1 sachet of 2.5% (w/v) Weedol or < 15 ml of 20% (w/v) concentrate]. Patients suffer vomiting and diarrhoea and develop generalized symptoms indicative of systemic toxicity. Pulmonary fibrosis develops in all cases but recovery may occur. In addition, renal failure and, sometimes, hepatic dysfunction may supervene. Death occurs in the majority of cases but can be delayed for 2 or 3 weeks.

Group 3

Acute fulminant poisoning follows the ingestion of more than (usually considerably in excess of) 40 mg of paraquat ion/kg body weight [i.e. > 15 ml of 20% (w/v) concentrate]. In addition to nausea and vomiting, there is marked ulceration of the oropharynx with multiple organ (cardiac, respiratory, hepatic, renal, adrenal, pancreatic, neurological) failure. In this group, at least in our experience, the mortality is

100%. Death may occur within 24 h of the overdose but is never delayed for more than 1 week.

Oropharyngeal and gastrointestinal symptoms

Paraquat itself causes nausea, vomiting (rarely blood stained) and diarrhoea as a result of its local irritant action on the gut. PP796, a phosphodiesterase inhibitor added as an emetic to nearly all recent paraquat formulations, stimulates directly the vomiting centre after absorption. Granular preparations contain magnesium sulphate which increases the likelihood of diarrhoea. The corrosive action of paraquat causes patients who are moderately or severely poisoned to develop a burning sensation, soreness and pain in the mouth, throat, chest (retrosternally) and abdomen (usually epigastric and is sometimes associated with guarding). Ulceration in the mouth, sloughing of the oropharyngeal mucosa, an inability to swallow saliva ('pseudohypersalivation'), dysphagia and aphonia are common. Prominent pharyngeal membranes ('pseudodiphtheria') have been reported (Stephens *et al.*, 1981) and perforation of the oesophagus may result in mediastinitis, surgical emphysema (Figure 1) and pneumothorax.

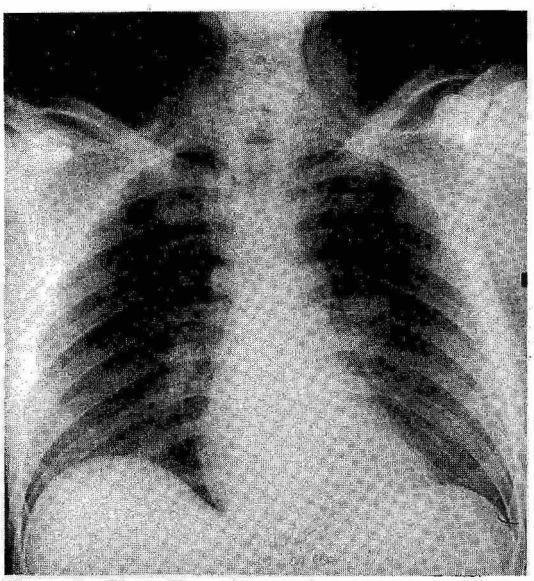

Figure 1 Chest X-ray in a patient who developed perforation of the oesophagus, mediastinitis and surgical emphysema

General symptoms

Within 24 h of ingestion patients in groups 2 and 3 develop lethargy, a widespread burning sensation, generalized weakness and myalgia, giddiness, headache, anorexia and fever. Fear and apprehension are prominent features and restlessness is sometimes observed.

Renal, hepatic and pancreatic symptoms

Oliguric or non-oliguric renal failure may supervene and is due usually to acute tubular necrosis though, exceptionally, glomerular and tubular haemorrhage may be found (Kodagoda *et al.*, 1973). Proximal tubular dysfunction which results in proteinuria, microscopic haematuria, glycosuria, aminoaciduria, phosphaturia and excessive leaking of sodium and urate is common (Vaziri *et al.*, 1979).

Jaundice, hepatomegaly and central abdominal pain due to pancreatitis, together with associated biochemical abnormalities are frequent complications in patients severely poisoned with paraquat. Centrilobular hepatic necrosis and cholestasis are seen at post mortem examination in these patients.

Respiratory features

Most patients develop a cough which may be productive and blood stained. Dyspnoea is a prominent feature and occurs early in those patients who have ingested a substantial amount and, in these circumstances, is due to the development of the adult respiratory distress syndrome. In less severely poisoned patients the onset of dyspnoea may be delayed and is then caused by pulmonary fibrosis. Rarely, pneumothorax (in association with mediastinitis), pleural effusion and iatrogenic pulmonary oedema, may precipitate dyspnoea.

In addition to a falling gas transfer factor (TLCO) and vital capacity (which may return to normal in patients in group 1 and, less commonly, in those in group 2), severely poisoned patients will have a low and falling P_{O_2} with resultant central cyanosis. Radiological changes do not always parallel the severity of clinical symptoms. Thus, the chest X-ray may be normal particularly in those dying early from multiple organ failure. More usually, patchy infiltration occurs (Figure 2) which may progress to an opacification of one (Figure 3) or both (Figure 4) lung fields.

Cardiovascular features

Except for sinus tachycardia, cardiovascular complications are not usually observed until the terminal phase of intoxication. Then, ventricular tachycardia, intraventricular conduction disturbances, and non-specific T-wave changes on electrocardiogram occur. Sinus bradycardia, hypotension and cardiac arrest may supervene. The chest X-ray may show massive cardiomegaly and, at post mortem, toxic myocarditis is found histologically.

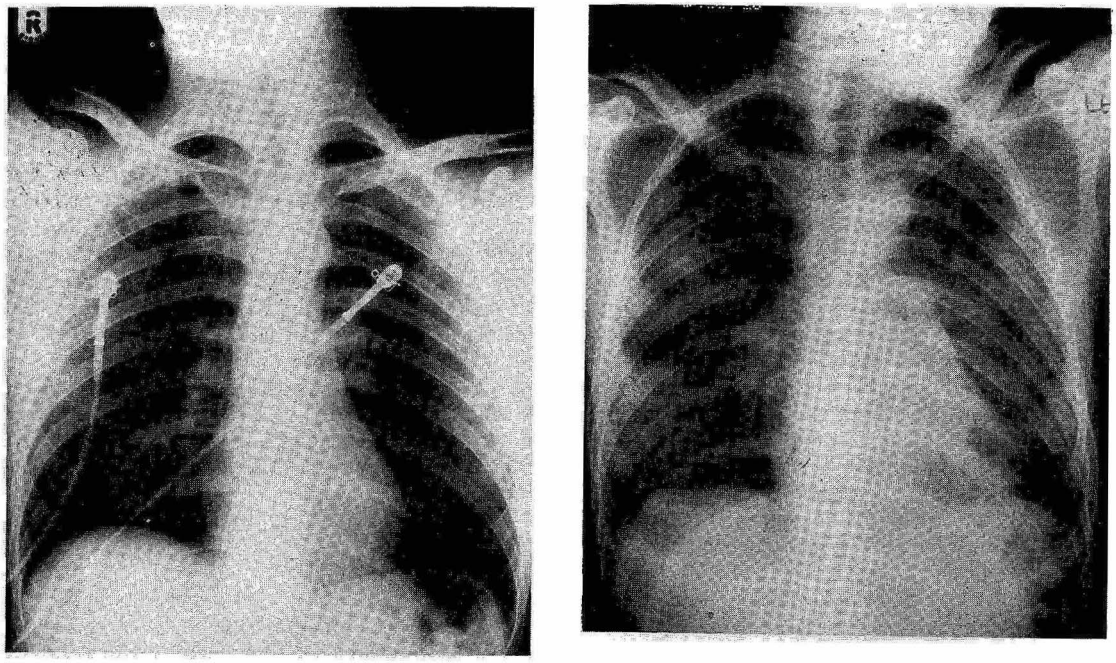

Figure 2 Chest X-ray on admission (**a**) and 15 days later (**b**) showing patchy infiltration in both lung fields

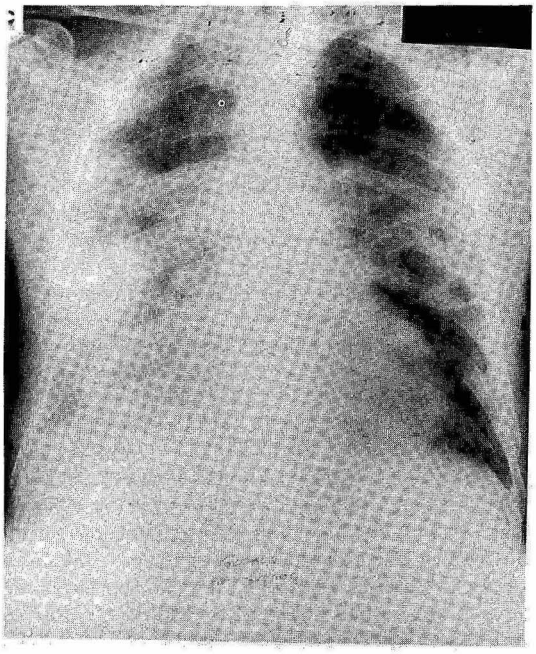

Figure 3 Chest X-ray showing patchy infiltration in both lung fields with partial opacification of the right

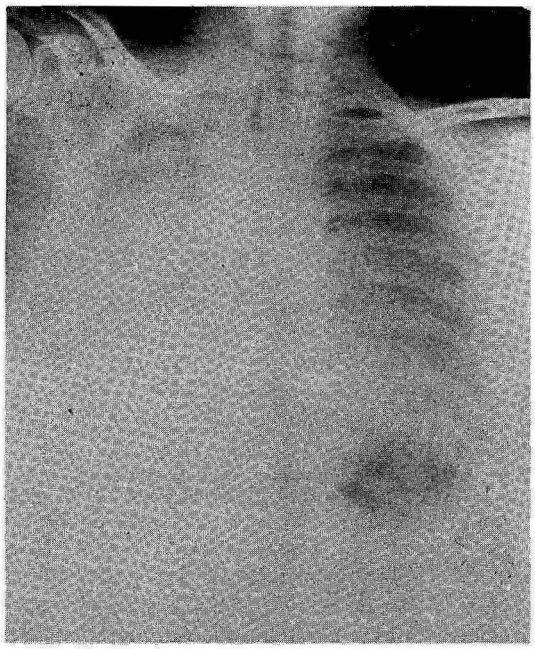

Figure 4 Chest X-ray showing total opacification of the right lung field and partial opacification of the left field

Neurological features

Coma is a common and terminal event, though other neurological features such as ataxia and facial paresis (Almog & Tal, 1967) are occasionally observed. Convulsions have been reported (Mickelson & Fulton, 1971; Conradi *et al.*, 1983; Addo *et al.*, 1984) and may be due to cerebral oedema (Grant *et al.*, 1980) precipitated by fluid overload (Fennelly *et al.*, 1971).

Adrenal cortical necrosis

At post-mortem examination adrenal cortical necrosis is often observed (Nagi, 1970; Kodagoda *et al.*, 1973; Reif & Lewinsohn, 1983) particularly in severely poisoned patients with multiple organ failure (group 3). The clinical significance of this observation is unclear since the use of corticosteroids does not correct hypotension, which is more probably due to myocardial failure.

Haematological and biochemical abnormalities

A polymorphonuclear leucocytosis is a frequent finding but, rarely, erythrocyte aplasia, leading to a normochromic anaemia (Lautenschlager *et al.*, 1974) and haemolytic anaemia (Fairshter *et al.*, 1976) have been reported. Metabolic acidosis, probably secondary to cardiovascular collapse and hypoxia, is a common complication. Hypocalcaemia, which sometimes results in tetany, is usually iatrogenic after either inappropriate attempts at forced diuresis in the presence of renal impairment (Fennelly *et al.*, 1971) or charcoal haemoperfusion (Siefken, 1982). In addition, elevation of serum creatinine kinase activity is seen, secondary to paraquat-induced muscle damage.

General management

Initial management has four priorities. Firstly, fluid loss should be replaced; secondly, the prognosis should be determined; thirdly, symptoms due to ulceration of the oropharynx must be relieved; fourthly, appropriate supportive care for patients and relatives must be provided. In addition, it may be appropriate to consider referral to a specialist treatment centre.

The value of methods to prevent absorption are discussed critically in a separate paper (Meredith & Vale, 1987).

Fluid replacement

There is good evidence that, as a result of vomiting and diarrhoea and the administration of purgatives, many patients poisoned with paraquat are fluid depleted (Williams *et al.*, 1984). An intravenous infusion should therefore be commenced on admission to reduce the risk of renal dysfunction and diminished renal excretion of paraquat.

Assessment of prognosis

The history is a good general guide in that the ingestion or injection of the 20% (w/v) paraquat concentrate will invariably lead to severe poisoning. If a granular preparation has been ingested, a qualitative urine test should be performed with alkaline sodium dithionite (Braithwaite, 1987). If this test is negative within 24 h of the overdose there is no clinical need for a quantitative assay on the blood and the patient may be reassured accordingly. If, however, the urine test is positive, measurement of the plasma paraquat concentration is extremely helpful and may be interpreted by reference to published data (Proudfoot *et al.*, 1979; Hart *et al.*, 1984; Scherrmann *et al.*, 1987).

Referral to a specialist centre?

If the diagnosis of paraquat poisoning is confirmed, the decision as to whether to refer the patient to a specialist poisons treatment centre should be taken. At least in the UK, the majority of doctors and nurses at local hospitals have not managed personally a case of severe paraquat poisoning and this lack of clinical experience, combined with the knowledge that the mortality is high, engenders a feeling of uncertainty in the staff concerned which is often then recognized by patients and relatives. In contrast, a specialist centre will have considerable medical and nursing expertise available not only to relieve the local and systemic effects of paraquat poisoning but also to employ elimination techniques if appropriate (Proudfoot *et al.*, 1987).

Referral to a treatment centre may make visiting for the relatives difficult and arrangements must be made for relatives to stay in the hospital if they so wish. Our experience suggests that relatives are comforted by the fact that 'everything has been done' to make the patient's final days as comfortable as possible and this overrides any geographical inconvenience. At the same time it must be recognized that nursing staff in a specialist unit may themselves be distressed by the high mortality among patients poisoned with paraquat. In addition nurses who see themselves as intensive- or critical-care specialists may not welcome the need to practice terminal care.

Terminal care: relief of local pain and general distress

It is of vital importance that the patient is not neglected or isolated. Frequent visits from medical and nursing

staff are mandatory as bad or infrequent communication causes considerable suffering to the patient. Those who are dying reach out for support and companionship not only from their friends and relatives but from their medical advisers too. If asked, one should be honest about the prognosis, whilst at the same time offering hope. For 'the aim is to make dying a little easier, not to apply the dogma of always divulging the truth' (Hinton, 1967). It is reassuring to explain to the patient that 'we have managed patients like you before. No matter what happens we shall stand by you — we will not let you down'. This confident and supportive attitude reduces fear and despair. Above all, attention should be directed away from incurable organ damage to the alleviation of symptoms as there is always something that can be done to provide symptomatic relief.

Pain and distress should be reduced to a minimum. It is difficult to abolish the severe pain produced by local ulceration. Mouth washes, ice-cold fluids (e.g. ice-cream, lemon mucilage), local anaesthetic sprays and lozenges have all been employed with varying degrees of success. Opiates will be required eventually in most patients to relieve general, as well as local, pain and distress. Above all, inappropriate treatment should be avoided. Thus, for example, the repeated use of cathartics when the outlook is hopeless is therapeutically irrelevant and clinically harmful. One needs to remember that 'the emotional isolation of the dying may be diminished if all who care for him are aware of the problem and treat the patient with kindness, understanding and as an intelligent adult capable of adjusting to the truth.' (Twycross, 1975).

Managing the relatives

Relatives want and need an authoritative prognosis which it is now possible to give. Yet hope should not be removed completely, because the relatives need help to adjust to the probable death of the patient. It is appropriate and worthwhile to encourage the relatives to talk about the patient and to assist them, if necessary, to heal or reinforce their relation with the patient. Occasionally, relatives must be reminded that the patient's trust cannot be compromised by deceit when they insist that the patient is not told the truth about his illness.

The authors offer their thanks to nursing colleagues who have helped them to manage patients and their relatives.

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Treatment of Paraquat Poisoning in Man: Methods to Prevent Absorption

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Theoretically, absorption of an ingested dose of paraquat may be reduced by (1) gastric lavage, (2) induced emesis, (3) whole-gut lavage or (4) by the oral administration of adsorbent substances.

1 Animal experiments suggest that paraquat is absorbed poorly from the stomach and absorbed incompletely (< 5%) from the small intestine over a 1–6-h period. Although gastric lavage would therefore seem a logical way to ameliorate the toxicity of an ingested dose of paraquat, peak plasma concentrations are attained rapidly and evidence for the efficacy of gastric lavage in man is poor.

2 In 1977, a potent emetic (PP796) was added to liquid and solid formulations of paraquat because experiments in primates had demonstrated a fivefold reduction in toxicity. In man, ingestion of formulations containing an emetic is more likely to cause spontaneous vomiting within 30 min than non-emetic preparations. However, definite evidence of benefit, as judged by improved patient prognosis, has yet to be established.

3 Gut lavage has been shown to remove only a small proportion of an ingested dose of paraquat. At the flow rates employed in man (75 ml/min), approximately 0.5–1.0 litres of lavage fluid/h may be absorbed across the intestinal wall. Since there is a theoretical risk of increasing paraquat absorption, the use of whole-gut lavage cannot be recommended.

4 Bipyridilium herbicides are adsorbed by soil and clay minerals, and montmorillonite in particular has been shown to be a strong binding agent *in vitro*. Accordingly, the use of Fuller's Earth (calcium montmorillonite) and Bentonite (sodium montmorillonite) for the treatment of poisoning has been investigated in animal models. Both agents reduce plasma paraquat concentrations and mortality in animals when administered after an oral dose of paraquat. Recently, other adsorbent materials have been found to have high maximum adsorption capacities for paraquat. In particular, activated charcoals and cation-exchange resins have attracted interest. Unfortunately, as yet, there is no evidence that the use of adsorbents in man is of therapeutic value.

Introduction

Paraquat (1,1-dimethyl-4,4-bipyridilium) is a potent contact herbicide that is potentially lethal to man if ingested. Death due to paraquat poisoning is usually characterized by pulmonary oedema and fibrosis but, if large amounts are ingested, multiple organ failure may develop (Vale *et al.*, 1987). The precise mechanism of toxicity is uncertain but, once a critical plasma concentration is exceeded, active accumulation of paraquat in the lung occurs, with formation of superoxide anion and depletion of NADPH (Smith, 1987). There is no effective antidote for paraquat poisoning (Bateman, 1987) and measures designed to enhance the elimination of paraquat from the body have not proven satisfactory (Bismuth *et al.*, 1987; Proudfoot, 1987). Attention has therefore been directed at the various means by which the absorption of an ingested dose of paraquat may be either prevented or reduced, namely gastric lavage, induced emesis, whole-gut lavage or the oral administration of adsorbent substances. The rationale for the use of each form of treatment is considered below and the evidence for their value in man is reviewed critically.

Gastric lavage

Paraquat is absorbed incompletely from the gut and, in man, it has been estimated that less than 5% of

an ingested dose is absorbed over a 1–6-h period (Conning *et al.*, 1969). Animal experiments suggest that paraquat is absorbed poorly from the stomach but that facilitated absorption takes place in the small intestine. Thus, Smith *et al.* (1974) found that 10–40% of an orally administered dose remained in the rat stomach at 16 h. In the same study, a linear relation was noted between the paraquat content of the small intestine and the plasma concentration of paraquat. No such relation was observed between the paraquat content of the stomach and the plasma paraquat concentration. Bennett *et al.* (1976) demonstrated dose-dependent absorption in greyhound dogs. When propantheline, an anticholinergic drug which delays gastric emptying, was administered intravenously 15 min before an oral dose of paraquat, the time at which the peak plasma concentration of paraquat occurred was shifted from 75 min to 3–6 h.

Paraquat absorption from the gut may be incomplete but it is rapid, as evidenced by the time at which peak plasma concentrations are observed in different animal species. For example, peak concentrations occur in guinea pigs at 60 min (Conning *et al.*, 1969), in cats at 60 min (Clark, 1971) and in dogs at 60–75 min (Bennett *et al.*, 1976; Nakamura *et al.*, 1982). In man, the time at which the paraquat concentration in plasma peaks is not known with certainty. However, paraquat may be detected in the urine as early as 1 h after ingestion of an overdose and, to judge by the plasma concentration data published by Proudfoot *et al.* (1979), peak concentrations in man are certainly attained within 4 h. Active accumulation of paraquat by lung tissue and subsequent toxicity occurs once a threshold plasma concentration is exceeded. To be effective therefore gastric lavage, and other methods used to reduce absorption, must be employed sufficiently early to blunt or abolish the rapid rise in the plasma paraquat level so that the threshold concentration is not achieved.

Surprisingly, there is very little experimental information relating to the use of gastric lavage alone in the treatment of paraquat poisoning. As part of a study to determine the effect of single dose administration of oral adsorbents, Clark (1971) gave four cats 62.5 mg of paraquat/kg by stomach tube and then performed gastric lavage 60 min later. A 'marked reduction in the levels of paraquat in the blood' was reported in comparison with untreated control animals. However, scrutiny of the data suggests that the reduction in blood paraquat concentrations achieved was only from 16 to 12 mg/l at 5 h after dose administration.

The role of gastric lavage in the treatment of all forms of poisoning in man has been questioned recently since the evidence for its value is poor. Proudfoot (1984), in a review of the subject, considered seriously whether use of the procedure should be abandoned. Kulig *et al.* (1985) undertook a prospective study of 592 patients admitted over an 18-month period to Denver General Hospital following the ingestion of a drug overdose. Gastric lavage was not found to be helpful in the majority of patients, although it did appear to be of some value in 'obtunded' patients provided that it was undertaken within 1 h of ingestion of the overdose.

So far as the treatment of paraquat poisoning is concerned, there have been only two clinical studies published where the authors have made specific mention of the efficacy of gastric lavage. Bismuth *et al.* (1982), in a review of 28 patients, were not able to establish the value of gastric lavage. Bramley & Hart (1983), in a study of 262 cases of paraquat poisoning in the UK, were unable to demonstrate an improved prognosis resulting from the use of gastric lavage. There are further theoretical objections to a stomach washout following the ingestion of paraquat. Ulceration of the oropharyngeal and oesophagogastric mucosal surfaces by concentrated formulations of paraquat can make the procedure hazardous. Furthermore the use of gastric lavage may delay the deployment of alternative forms of treatment with greater theoretical value, for example, administration of oral adsorbents.

In conclusion therefore there is no definite evidence of the value of gastric lavage in the treatment of paraquat poisoning in man and any possible benefit is likely to be confined to use within 1 h of ingestion.

Induced emesis

In 1977, the manufacturers of paraquat (Imperial Chemical Industries PLC) added a potent emetic, PP796, a phosphodiesterase inhibitor, to liquid and solid formulations of paraquat because experiments in primates (T. B. Hart, personal communication) had demonstrated a fivefold reduction in toxicity.

There are a few published laboratory experiments relating to the use of emetic formulations of paraquat, and the principal source of data is a study, undertaken by Nakamura *et al.* (1982), designed originally to investigate the efficacy of gut lavage. Eleven mongrel dogs were given paraquat (250 mg/kg) by stomach tube. Five dogs were given an emetic preparation and all vomited within 15 min; six dogs received a non-emetic preparation of paraquat and vomited approximately 1 h later. The upper duodenum and rectum of each dog were ligated under general anaesthesia 4 h after the administration of paraquat; the gut was then lavaged through a duodenostomy and the lavage fluid collected through a sigmoidostomy. Plasma paraquat concentrations were not reduced significantly in the group of dogs that received the emetic formulation of paraquat (Table 1). Moreover, for reasons that were unclear, the percentage recovery of the administered

Table 1 Plasma concentrations of paraquat (mg/l)[a] in dogs following the administration of emetic/non-emetic formulations [adapted from K. Nakamura, M. Yamashita & H. Naito (1982) *Vet. Hum. Toxicol.*, **24** (Suppl.), 157–158]

Group	*1 h*	*2 h*	*4 h*
Paraquat alone ($n = 6$)	122.7 ± 73.1	82.3 ± 41.6	52.9 ± 36.2
Paraquat + emetic ($n = 5$)	124.5 ± 43.9*	72.9 ± 40.8*	23.7 ± 6.7*

[a] Mean ± SD
* Not significant

dose of paraquat was strikingly small in both groups of dogs (paraquat alone 4.3 ± SD 4.5%; paraquat + emetic 2.5 ± 1.0%).

Following the introduction of emetic preparations of paraquat, the London Centre of the National Poisons Information Service (NPIS) and ICI Plant Protection Division conducted jointly a survey of paraquat poisoning in the UK. The study commenced in 1980 and interim results for 262 patients were reported in 1983 (Bramley & Hart, 1983). The presence, or absence, of the emetic in the preparation of paraquat ingested was established in 103 of 262 cases, and the time at which spontaneous vomiting occurred was known in 61 of 103 patients (Table 2). There can be no doubt that ingestion of the emetic formulation induces earlier vomiting, and the difference between the number of patients in each group (emetic v. non-emetic) who vomit either before or after 30 min (or not at all) is highly statistically significant (χ^2 9.87 corrected for continuity; $P < 0.005$). Furthermore, with the preliminary reported results of the survey, it is possible to show that, in the manner of a dose–response curve, vomiting is more likely to occur the greater quantity of paraquat ion ingested (Table 3). Unfortunately, despite the occurrence of earlier vomiting, Bramley & Hart (1983) were unable to demonstrate an improved prognosis in patients who had ingested emetic, rather than non-emetic, formulations of paraquat. Subsequent reports (Denduyts-Whitehead *et al.*, 1985; Onyon & Volans, 1987) from the same study have suggested a small, but inconclusive, fall in mortality since the introduction of the emetic, PP796. A reduction in the mortality from paraquat poisoning as a result of the emetic preparation has not been noted by other workers (Bismuth *et al.*, 1982; Nakamura *et al.*, 1982; Naito & Yamashita, 1987).

Thus far, then, it has not been possible to prove that any clinical benefit has derived from the introduction of emetic formulations of paraquat. In some ways, though, this is not surprising for there is, increasingly, doubt about the value of induced emesis as a means of treating any other form of intoxication (Corby *et al.*, 1968; Boxer *et al.*, 1969; Neuvonen *et al.*, 1983; Curtis *et al.*, 1984; Kulig *et al.*, 1985).

Whole-gut lavage

Published laboratory data on whole-gut lavage are confined to the study, mentioned above, by Nakamura *et al.* (1982). Eleven mongrel dogs were given paraquat (250 mg/kg) by stomach tube. Gut lavage was performed 4 h later and only 2.5–4.3% of the administered dose of paraquat was recovered. To explain

Table 2 Time of spontaneous vomiting after ingestion of emetic/non-emetic formulations of paraquat [adapted from A. Bramley & T. B. Hart (unpublished data)]

	Vomiting		
Group	*< ½ h*	*> ½ h*	*No vomiting*
Non-emetic formulation ($n = 21$)	4(19)	4(19)	13(62)
Emetic formulation ($n = 40$)	26(65)	9(22)	5(13)

Percentages are given in parentheses
$P < 0.005$ (see the text for details)

Table 3 Incidence of spontaneous vomiting 30 min after the ingestion of emetic/non-emetic formulations of paraquat [adapted from A. Bramley & J. B. Hart (unpublished data)]

	Amount of paraquat ion ingested (g)		
Group	*< 2*	*2–5*	*> 5*
Non-emetic formulation ($n = 21$)	1/10 (10)	1/4 (25)	2/7 (29)
Emetic formulation ($n = 40$)	16/29 (55)	3/4 (75)	7/7 (100)

Percentages are given in parentheses

the extremely low recovery of paraquat, it was hypothesized that either absorption must have occurred rapidly from the small intestine (peak plasma concentration ≤ 60 min; see Table 1), or that a substantial amount of paraquat must have remained in the stomach.

The only clinical report of whole-gut lavage where the procedure was used alone, without concomitant oral adsorbents, is that of Okonek *et al.* (1976). A 30-year-old male ingested an unknown quantity of Reglone (200 g of diquat/l) 30 h before admission. Whole-gut lavage was undertaken by using an electrolyte solution (6.14 g of NaCl/l, 0.75 g of KCl/l, 2.94 g of $NaHCO_3$/l) heated to body temperature which was fed into the patient by using a stomach tube and peristaltic pump. Approximately 27 mg of diquat was recovered in 6900 ml of lavage fluid. However, at the pumping rate employed (75 ml/min), it was found that 0.5–1.0 litres of lavage fluid were absorbed across the intestinal wall. Theoretically, this is likely to enhance absorption of diquat (or paraquat). Perhaps for this reason no subsequent studies have been reported using gut lavage alone. Certainly, there is no evidence to suggest that whole-gut lavage is of value in the treatment of paraquat poisoning in man.

Oral adsorbents

Bentonite and Fuller's Earth

In the period, 1965–1967, bipyridilium herbicides were found to bind strongly to soil and to clay minerals, in common with many other organic cations (Knight & Tomlinson, 1967). Study of the adsorption capacity and chemical composition of a variety of soils showed that montmorillonite in particular was a strong binding agent *in vitro* (Knight & Tomlinson, 1967).

Clark (1971) investigated the effect of single-dose administration of oral adsorbents on paraquat toxicity in animals. Preliminary experiments *in vitro* showed that the adsorption capacity of minerals varied, but that Bentonite (sodium montmorillonite) and Fuller's Earth (calcium montmorillonite) were particularly effective (Table 4). At the time that these experiments were undertaken and, for some years subsequently, emphasis was placed on the so-called strong adsorption capacity (SAC) of a substance. SAC is defined as the quantity of paraquat that can be adsorbed per unit weight of adsorbent before the adsorbent phase is in equilibrium with a detectable solution concentration (Knight & Tomlinson, 1967), in this instance 1 mg/l. In other words, there is a region of the adsorption isotherm in which paraquat cannot be detected in solution (this region has no physical significance but depends on the sensitivity of the analytical methods employed). The maximum adsorption capacity (MAC) of a substance (see below) is defined as the maximum quantity of paraquat that can be adsorbed per unit weight of adsorbent.

Clark (1971) went on to demonstrate that a single dose of adsorbent material administered to rats after a potentially lethal dose of paraquat could reduce mortality (Table 5). Bentonite and Fuller's Earth prevented some deaths even when administration was delayed for 3 h after dosing with paraquat. Further experiments in cats showed that some reduction in blood paraquat levels could be achieved following a single dose of either Fuller's Earth or Bentonite when compared with control animals (Clark, 1971).

Smith *et al.* (1974) investigated subsequently the effect of repeated doses of oral adsorbents on paraquat toxicity in animals. Rats were given four doses of a castor oil/magnesium sulphate/Bentonite mixture at 2–3-hourly intervals commencing 4–10 h after the oral administration of a lethal dose of paraquat (680 μmol/kg). Even when administration of the adsorbent/cathartic mixture was delayed for as long as 10 h, the mortality was considerably reduced.

Table 4 Strong adsorption capacities (SAC) of various minerals [adapted from D. G. Clark (1971) *Br. J. Indust. Med.*, **28**, 186–188]

Adsorbent	*SAC[a] (g of paraquat/100 g)*
Kaolin	0.5
Decalso[b]	1.4
Amberlite	1.7
Bentonite	5.0
Fuller's Earth	5.0

[a] Calculated on the basis of a 1 mg/l limit of detection
[b] Synthetic sodium aluminium silicate

Table 5 Mortality in rats due to paraquat following delayed administration of adsorbent materials [adapted from D. G. Clark (1971) *Br. J. Indust. Med.*, **28**, 186–188]

Adsorbent	*Time after dosing (h)*	*Paraquat dose and mortality[a] (mg/kg)*	
		200	*300*
None	—	6/6	6/6
Amberlite	0.5	6/6	6/6
Decalso	0.5	6/6	6/6
Bentonite	0.5	0/6	6/6
	1.0	0/6	6/6
	2.0	3/6	6/6
	3.0	5/6	6/6
Fuller's Earth	0.5	0/6	3/6
	1.0	1/6	6/6
	2.0	2/6	5/6
	3.0	4/6	6/6

[a] LD_{50} in rats 150 mg/kg

Twenty-seven of 29 untreated control rats died, but not one of 10 rats died when treated at 4 h, and only two of 10 rats died when treated at 10 h after administration of the paraquat. Smith *et al.* (1974) were able to show that the reduction in mortality was associated with a concomitant reduction in the plasma concentration of paraquat and a reduction in the amount of paraquat accumulated in lung tissue.

Fuller's Earth is preferred in clinical practice because it can be used as a 30% (w/v) suspension, whereas Bentonite swells in water and can only be used as a 6 or 7% (w/v) suspension. Magnesium sulphate is usually administered at the same time as the adsorbent to increase the rate of elimination of the Fuller's Earth/Bentonite–adsorbed paraquat complex from the gut. Unfortunately, the use of these agents in poisoned patients has not met with the same success as in laboratory experiments. Thus, Park *et al.* (1975) gave 11 patients a 7% (w/v) Bentonite suspension, six of whom subsequently died; nine of 10 patients treated with 30% (w/v) Fuller's Earth by Vale *et al.* (1979) also died; 18 of 26 patients died in Belfast following the administration of Fuller's Earth (Coppel *et al.*, 1981); in Paris, 10 of 13 patients died despite being given a 15% (w/v) suspension of Fuller's Earth (Bismuth *et al.*, 1982). Finally, Bramley & Hart (1983), in a review of 262 cases of paraquat poisoning in the UK, were unable to demonstrate an improved prognosis associated with the use of Fuller's Earth. In this latter study, though, almost all patients received Fuller's Earth and the control group was too small.

Activated charcoal

At the time that Clark (1971) undertook his experiments with adsorbent substances in rodents, the assumption was made that activated charcoal would not bind paraquat. It is only recently that this assumption has been challenged and found to be false. Okonek *et al.* (1982) have shown *in vitro* that activated charcoal, despite having a low SAC, possesses a maximum binding capacity greater than that of either Fuller's Earth or Bentonite (Table 6). They also undertook experiments *in vivo*, using rats, similar to those of Clark (1971). A single 1-g dose of adsorbent was instilled by mouth at various times after the administration of a lethal dose of paraquat. Activated charcoal (Kohle-Compretten, Merck) effected a reduction in mortality greater than that achieved by either Fuller's Earth or Bentonite (Table 7).

Other workers have investigated the effect of single dose administration of activated charcoal in mice (Gaudreault *et al.*, 1985). Not only did activated charcoal appear to be effective, but the addition of a cathartic agent (magnesium citrate) increased the chances of survival in these experiments (Table 8).

Table 6 Maximum (MAC) and strong (SAC) adsorption capacities of various materials [adapted from S. Okonek, H. Setyadharma, A. Borchent & E. G. Krienke (1982) *Klin. Wochenschr.*, **60**, 207–210]

Adsorbent	*MAC (g of paraquat/ 100 g)*	*SAC[a] (g of paraquat/ 100 g)*
Fuller's Earth	6	5
Fullererde	2	<1.0
Bentonite	6	5
Bentonit APV	6	4–5
Bentonit SF	6	5
Activated charcoal (Kohle-Compretten, Merck)	>8	<1.0

[a] Calculated on the basis of a 0.5 mg/l limit of detection

Table 7 Mortality in rats due to paraquat following delayed administration of adsorbent materials [adapted from S. Okonek, H. Setyadharma, A. Borchent & E. G. Krienke (1982) *Klin. Wochenschr.*, **60**, 207–210.

Adsorbent	*Time after dosing (h)*	*Paraquat dose and mortality[a] (mg/kg)*	
		200	*300*
None	—	6/6	—
Fuller's Earth	0.5	0/6	6/6
	1.0	0/6	6/6
	2.0	1/6	6/6
	3.0	1/6	6/6
Bentonit APV	0.5	0/6	4/6
	1.0	2/6	5/6
	2.0	0/6	6/6
	3.0	0/6	6/6
Activated charcoal (Kohle-Compretten, Merck)	0.5	0/6	2/6
	1.0	0/6	4/6
	2.0	0/6	4/6
	3.0	2/6	5/6

[a] LD_{50} in rats 150 mg/kg

Table 8 Mortality in mice due to paraquat (200 mg/kg) followed by single dose treatment 30 min later [adapted from P. Gaudreault, P. A. Friedman & F. H. Lovejoy (1985) *Ann. Emerg. Med.*, **14**, 123–125]

Group	*Mortality*
No treatment	11/16
Magnesium citrate	5/16
Fuller's Earth	6/16
Activated charcoal	6/16
Activated charcoal + magnesium citrate	1/6[a]

[a] $P < 0.01$

The type of activated charcoal employed was not stated.

It is important to recognize that not all forms of activated charcoal have the same capacity to adsorb paraquat (Table 9), a factor that may have some importance if poisoned patients are to be treated with this material rather than Fuller's Earth or Bentonite. However, results of multiple-dose administration of activated charcoal in the treatment of paraquat toxicity have not yet been reported for either animals or man.

Cation exchange resins

Recently, some interest has centred on cation exchange resins, normally used for the treatment of hypercalaemia, as an alternative means of binding paraquat in the gut to reduce systemic adsorption. Kayexalate (sodium polystyrene sulphate) and Kalimate (calcium polystyrene sulphate) have high MAC for paraquat (Table 9), and Nokata *et al.* (1984) have reported a reduction in morbidity in rats from paraquat toxicity following the delayed administration (up to 24 h) of these materials. Latterly, Yamashita *et al.* (1987) have reported the results of gastric and intestinal lavage with these materials in 22 patients. Six of 11 patients treated in this manner survived, but 11 patients who did not receive Kayexalate died. Unfortunately, it is not possible to judge whether the severity of poisoning was comparable in the two groups of patients because blood concentration data are not provided.

In conclusion then, so far as oral adsorbents are concerned, there is no definite evidence of their value in man for the treatment of paraquat poisoning. Nevertheless, the MAC of some activated charcoals are greater than those of either Fuller's Earth or Bentonite. As a means of reducing the absorption of drugs, though, activated charcoal has never been shown to reduce either the morbidity or mortality of any form of poisoning. In contrast repeated oral doses of activated charcoal may enhance the elimination of certain drugs, e.g. phenobarbitone (Berg *et al.*, 1982) whose toxic effects are then ameliorated as the blood concentration falls. Obviously, this situation is very different from that which obtains in paraquat poisoning.

Table 9 Maximum adsorption capacities (MAC) of activated charcoals and other materials [adapted from T. B. Hart, (personal communication)]

Adsorbent	*MAC (g of paraquat/100 g)*
Carbomix	9–10
Ultracarbon	8–9
Amoco AC	> 8
Medicoal	> 6
Norit AC	6
SK & F AC	< 1
Fuller's Earth	6
Kayexalate[a]	> 10
Kalimate[b]	> 10

[a] Sodium polystyrene sulphate
[b] Calcium polystyrene sulphate

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Pharmacological Treatments of Paraquat Poisoning

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1 A large number of pharmacological techniques aimed at modifying paraquat toxicity have been investigated. There is no convincing controlled evidence that any are unequivocally useful.
2 Studies with an ascorbic acid and riboflavin combination appear effective in rats, and there is a suggestion that cyclophosphamide and dexamethasone may in some way alter paraquat toxicity in man and by pretreatment, but not concurrent treatment, also in the rat.
3 Further controlled studies are required of these treatments in patients who are potentially salvageable. There is a need for a rapid paraquat assay for clinical use in order that patients in this category can be identified quickly and included in appropriate controlled studies.

Introduction

Although 'antidotes' to toxins are usually well remembered by medical students, there is no true pharmacological antagonist for the vast majority of poisons. In the case of paraquat poisoning although no antidote exists, a variety of treatments have been advocated over the past 20 years.

The use of a pharmacological treatment for a poison usually derives from basic knowledge of the mechanism by which the toxic effects of the poison are mediated. Drugs may then be used in an attempt to achieve a variety of therapeutic effects including: (a) antagonism of a pharmacological effect of the poison (true pharmacological antagonism); (b) reversal of a physiological effect of the poison; (c) alteration of the tissue distribution of the poison, for example, by competing with membrane pumps; (d) alteration of biochemical pathways and hence the biochemical response to a poison; (e) chelation with a poison to deactivate it; (f) alteration of the pathological response to tissue damage caused by the poison.

In the case of paraquat much experimental work has been performed to evaluate potential therapies for poisoning in animal species. In patients, however, there has been little attempt to systematically assess therapy. This is partly because the clinical features of paraquat poisoning relate to the dose taken and for the liquid concentrate death is often extremely rapid with the larger doses that are consumed. In contrast we also see a group of patients who take a dose of paraquat that will do them no harm. Attempts to assess the benefits of therapy need therefore to be addressed to a specific group of patients who are potentially salvageable. These may perhaps be identified by plasma paraquat concentrations (Proudfoot *et al.*, 1979; Hart *et al.*, 1984) or urinary paraquat excretion rates (Wright *et al.*, 1978).

Such studies that exist suggest that at the present time dose rather than any subsequent treatment is the principal determinant of survival in paraquat poisoning (Hart, 1985). A final important difficulty is that most treatment centres see only a relatively small number of patients making accurate scientific study difficult.

Assessment of literature reports of claimed beneficial effects of treatment for paraquat poisoning therefore requires adequate information on the plasma paraquat concentration in patients treated. Unfortunately, this information is often lacking, particularly with reports before the mid 1970s.

Specific therapies

Attempts to modify the toxicity of paraquat have involved most of the potential techniques mentioned in the introduction although there is no true pharmacological antagonist for paraquat and there are no chelating agents capable of binding the drug in the blood.

Reversal of physiological effects

Fluid replacement. Two separate groups of workers have pointed out the fact that many patients presenting after paraquat poisoning are dehydated, often as a result of vomiting (Webb & Leopold, 1983; Williams *et al.*, 1984). Although these workers reasonably advocate fluid replacement in such patients they present no evidence that this protects against para-

quat toxicity or prolongs life. Indeed the two patients reported by Webb & Leopold both died. Similarly, the use of diuretics to maintain urinary flow has not been shown to be beneficial.

Alteration in tissue distribution

Emetic additive. In 1979 ICI introduced an emetic into preparations of paraquat in the UK. This was on the basis of studies in animals suggesting reduced mortality (Denduyts-Whitehead *et al.*, 1985). The emetic used acts on the chemoreceptor trigger zone and thus has itself to be absorbed before it can act. The theoretical benefit of such an addition has never been shown clearly to reduce mortality in man, though the use of an emetic clearly should have potential benefit. It may also be a compounding factor in the assessment of newer therapies if the control group is a retrospective series.

Pump inhibitors. Work by a number of groups has been directed to finding agents that would inhibit the uptake of paraquat into lung, a phenomenon shown to be due to an energy-dependent process in 1974 (Rose *et al.*, 1974). This uptake process is likely to be the principal reason for the specific lung toxicity seen with paraquat. Ross & Krieger (1981) have reported on the structure–activity relation of this pump mechanism for a variety of amines and examined the ability of these compounds to interfere with paraquat uptake into lung. They noted that polyamines were more effective inhibitors than compounds containing only one quaternizable nitrogen. Diaminoalkanes were the most potent inhibitors they studied. In these studies *in vitro* the most effective pump competitor only inhibited paraquat uptake by about 75%, however, and none of their compounds would have yielded a maximal inhibition at a physiologically compatible concentration. It seems the pump that paraquat rides is normally used to take up circulating naturally occurring polyamines such as putrescine (Karl & Friedman, 1983).

There have been several studies showing that a number of other agents will reduce paraquat uptake into lung *in vitro* (Lock *et al.*, 1976; Maling *et al.*, 1978). Studies *in vivo* in animals have, however, in general, failed to demonstrate significant protection from paraquat (Maling *et al.*, 1978). Such protection as was afforded by propranolol did not seem to be due to pump inhibition (Maling *et al.*, 1978) and some other mechanism on the cell must be postulated, perhaps via increased levels of superoxide dismutase (Davies & Davies, 1974). Uncontrolled studies of D-propranolol in patients did not reveal evidence of therapeutic benefit (Fairshter *et al.*, 1976) although plasma paraquat concentrations were not assessed in patients treated.

Work in animals suggests that the toxicity of paraquat could be enhanced by β-adrenoceptor agonists and paraquat uptake *in vitro* reduced by β-adrenoceptor antagonists (Maling *et al.*, 1978). The mechanism of increased toxicity after β-adrenoceptor agonists appears to be reduced paraquat clearance, probably secondary to reduced renal blood flow, and was not reversed by D-propranolol, the isomer of propranolol which lacks β-adrenoceptor antagonist properties.

The use of putrescine, given at the same time as paraquat, has been investigated in rats (Dunbar *et al.*, 1985). Although the experiments were only on small numbers of animals putrescine co-administration reduced lung paraquat concentrations profoundly from 18 ± 7 ($n = 3$) to 0.3 ± 0.4 ($n = 2$) ng/mg of protein. This difference was, disappointingly, not accompanied by a reduction of biochemical evidence of paraquat damage as assessed by the lung glutathione and oxidized glutathione levels. Putrescine has not been used clinically, but the above findings suggest pump inhibitors do not present an attractive mode of therapy.

Reversal of biochemical damage

Since the effects of paraquat on the lungs are delayed after overdose it was realized quickly that secondary changes induced by paraquat were probably responsible for its late pulmonary toxicity.

The biochemical effects of paraquat have been reviewed by Onyeama & Oehme (1984) but can be considered simply as being due to paraquat effect on redox potential with the production of a superoxide ion, and singlet oxygen, together possibly with hydroxyl radicals. Lipid peroxidation is one mechanism by which cell damage is then produced (Bus *et al.*, 1976), but is probably less important with larger overdoses (Steffen *et al.*, 1980) in which other effects of paraquat on the cell supervene. NADPH depletion is an alternative mechanism of paraquat damage. Since paraquat is probably reoxidized and re-reduced in a cyclic manner the treatment of patients poisoned with paraquat should be prolonged. A variety of experimental approaches have been adopted in an attempt to reduce paraquat toxicity and they will be reviewed briefly.

Superoxide dismutase. This agent was first used on the basis that increasing the breakdown of excess superoxide would decrease paraquat toxicity. Superoxide dismutase was reported to be protective to experimental animals by Autor (1974). Other workers have not, however, found superoxide dismutase to be effective (Rhodes & Patterson, 1978; Frank, 1983) in experimental animals or to prevent the increased toxicity of paraquat associated with, for example, vitamin E deficiency (Block & Wasserman, 1978). In

patients with paraquat poisoning, infusions of superoxide dismutase have been used but without apparent clinical benefit. It has been suggested this is because the enzyme molecule is too large to enter the cell and thus cannot be expected to be of benefit (Frank, 1983). The use of liposomes might improve penetration of superoxide dismutase but has not been evaluated. We have used intrapulmonary superoxide dismutase, administered during fibre-optic bronchoscopy, into one lung in two patients, Recovery appeared similar in both lungs, and in neither case were severe features of poisoning present. There thus seems no rationale at present to use superoxide dismutase in the treatment of paraquat poisoning. Interestingly, pretreatment of rats with endotoxin and hypoxia increases superoxide dismutase levels, as does the administration of aspirin, indomethacin or hydrocortisone (Reddy *et al.*, 1976). This is associated with a decrease in paraquat mortality in rats. Such pretreatment is not feasible in patients.

Vitamin E. Vitamin E is a reducing agent and could act as a free-radical scavenger. There is experimental evidence that vitamin E-deficient animals are more susceptible to paraquat (Block & Wasserman, 1978; Bus *et al.*, 1976). Acute treatment with vitamin E in normal rats does not, however, appear to protect against acute poisoning (Redetzki & Wood, 1980) nor did dietary supplementation in chicks reduce paraquat toxicity (Combs & Peterson, 1983). Clinical studies are few. Shahar *et al.* (1980) reported recovery from paraquat poisoning in a child who had taken a potentially lethal dose of gramoxone (serum level 8.2 mg/l) but other reports do not suggest benefit (Harley *et al.*, 1977). The experimental evidence does not appear to support the use of vitamin E.

Ascorbic acid. Ascorbic acid is an anti-oxidant but manipulation of dietary ascorbate levels did not produce a significant alteration in the toxicity of paraquat in guinea pigs (Sullivan & Montgomery, 1984). Other studies have suggested ascorbic acid might either be protective (Matkovics *et al.*, 1980) or actually potentiate paraquat toxicity (McArn *et al.*, 1980; Montgomery *et al.*, 1982). In view of this mixed picture experimentally, ascorbic acid does not appear to have a clinical role.

Desferrioxamine. Desferrioxamine is a chelator of iron, which has been postulated as being important in the mechanism of paraquat toxicity. Studies in mice suggest that desferrioxamine given 24 h before, and regularly after, an acute dose of paraquat will reduce mortality (Kohen & Chevion, 1985). In the same experimental model iron increased paraquat toxicity. In rats, however, desferrioxamine seemed to increase paraquat toxicity, with an apparent worsening of pulmonary fibrosis in surviving animals, when it was given 2 h before and 7 days after paraquat administration (Osheroff *et al.*, 1985). There was, however, a suggestion of a dose effect of desferrioxamine in the mouse with high doses perhaps worsening toxicity (Osheroff *et al.*, 1985). This area would seem to merit further studies but desferrioxamine cannot be advocated in humans at the present time.

Selenium. Selenium is a co-factor for the enzyme glutathione peroxidase. Rats deficient in selenium are at greater risk of paraquat damage (Glass *et al.*, 1985) and dietary supplementation in the chick is protective (Combs & Peterson, 1983). There are, however, no clinical studies and it seems unlikely that selenium given after an overdose would be beneficial, since in the chick the amount of selenium that protects deficient chicks is less than that for maximal activity of the selenium-dependent enzymes (Anon., 1984).

Clofibrate. Clofibrate has been noted to increase hepatic catalase activity and it was postulated a similar effect in the lung might protect from paraquat toxicity. Pretreatment of rats with clofibrate for 6 days was significantly protective against paraquat although there was no significant change in the content of anti-oxidant enzymes in the lung. Administration of clofibrate after paraquat was not protective, however (Frank *et al.*, 1982), and the drug has therefore not been advocated for use in man.

Acetylcysteine. Animal studies with acetylcysteine as a sulphydryl donor antidote to paraquat in isolated rat hepatocytes suggested that it might be partially protective, but only in animals pretreated with phenobarbitone (Dawson *et al.*, 1984). Paraquat induced renal damage in rats was not reduced by acetylcysteine although the urinary excretion of paraquat was increased (Cramp, 1985). There seems no experimental evidence therefore to support the use of *N*-acetylcysteine in man and use in one of our own patients did not seem to produce clinical benefit.

Riboflavin and niacin. A combination of ascorbic acid and riboflavin in rats produced a significant improvement in paraquat mortality (Schvartsman *et al.*, 1984). None of 44 rats survived paraquat (200 mg/kg) but five of 44 survived with ascorbic acid (1 g orally). In a second experiment four of 46 rats treated with ascorbic acid survived but 24 of 53 treated with riboflavin (2 mg) and ascorbic acid survived. Riboflavin alone did not appear protective. The authors postulated these benefits as being due to the possible anti-oxidant effect of ascorbic acid together with an effect of riboflavin on glutathione reductase activity. Niacin resulted in a modest reduction in 7-day mortality in rats (Brown *et al.*, 1981) from 75 to 55%. This was

attributed to an effect of niacin in NAD synthesis which is reduced by paraquat. There have been no controlled human studies of the use of these vitamins reported in paraquat poisoning though some workers have included them in their regimens (Addo & Poon-King, 1987). This area seems to merit further work.

Techniques to prevent late lung sequelae

Since for many patients death from paraquat poisoning is delayed by several days and is due to the pulmonary effects of the agent, techniques to reduce the secondary toxicity of paraquat have been investigated. In clinical studies of single patients the effects of immunosuppressants have not been encouraging (Fennelly *et al.*, 1968; Malcolmson & Beesley, 1975) though other workers attributed survival to immunosuppressant use (Malone *et al.*, 1971; Laithwaite, 1975). Since plasma concentration measurements of paraquat were not made it is unclear whether immunosuppressant therapy made any difference to expected survival.

In the rabbit corticosteroids do not appear to protect against sub-lethal paraquat-induced lung damage (Seidenfeld, 1985). In these studies paraquat was given by inhalation and methylprednisolone (1 mg/kg) was the steroid used as pretreatment. Previous results in the rat were, in contrast, encouraging when prolonged oral hydrocortisone pretreatment was given (Reddy *et al.*, 1976). The benefit of steroids in paraquat overdose clinically thus remains in doubt.

It is of interest to consider more recent reports (Addo *et al.*, 1984; Addo & Poon-King, 1987) of the apparent benefit of cyclophosphamide and dexamethasone in paraquat poisoning in the West Indies. In their study 75% of a group of patients who consumed liquid paraquat preparations survived, compared with the same workers previous experience of 80% mortality (Rahaman & Poon-King, 1976) and the same usually expected high (60% or over) mortality from gramoxone preparations (Bismuth *et al.*, 1982). This work clearly requires further evaluation. Plasma paraquat level monitoring of some of the surviving patients does suggest that the paraquat concentrations (> 2 mg/l within 24 h of poisoning) were high enough to make death likely (Addo & Poon-King, 1987). A possible confusing factor is the introduction of emetic into paraquat sold in the West Indies in recent years and the fact that these workers have also included vitamin C and niacin in their treatment protocol (Addo & Poon-King, 1987). Work in the rat with cyclophosphamide and dexamethasone has suggested protection with a 2-day pretreatment, but not when paraquat was given simultaneously with cyclophosphamide and dexamethasone (Smith & Watson, 1987). The precise mechanism of this protective effect and whether it is due to either cyclophosphamide, dexamethasone or the combination require further study.

Other workers have suggested colchicine might have a role in the treatment of patients with pulmonary damage but this is on the basis of only one published report (Vincken *et al.*, 1981) and no plasma paraquat concentration measurements were quoted. An alternative approach attempted in animals has been the use of collagen synthesis inhibitors (Akahori & Oehme, 1983) L-3,4-dehydroproline and D,L-3,4-dehydroproline, but these were not effective in reducing paraquat lung damage in rat.

Conclusions

Since the first report of clinical poisoning with paraquat was published 20 years ago (Bullivant, 1966) there has been very little systematic clinical study of the use of pharmacological therapies for paraquat poisoning. Although much work has gone into the study of elimination techniques in paraquat poisoning there is reason to doubt the efficacy of such treatments in the majority of patients (Hart, 1985), particularly since there is often an inevitable delay between presentation and treatment.

In considering the treatment of paraquat poisoning it seems to the author high time that clinical trials of the sort successfully mounted in paracetamol poisoning be addressed. Clearly, these will have to be multicentre, if not multinational.

There is still a need for a technique of rapid plasma analysis of paraquat to delineate the patient who is at risk from paraquat injury but who is, at least potentially, salvageable. The author suggests that patients in the 30–80% mortality range (Hart *et al.*, 1984) should be considered for such studies. Single case reports are dangerous in perhaps both condemning potentially useful treatments or encouraging potentially toxic ones unnecessarily. The ideal pharmacological antagonist, one that would be added to the packet of Weedol or bottle of Gramoxone, seems as far away as ever.

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Elimination of Paraquat

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1 There is a striking discrepancy between the efficacy of the kidneys, haemodialysis and haemoperfusion in removing paraquat from the body and the poor prognosis of paraquat poisoning even when the blood and urine concentrations (which are good indices of concentrations in lung and other tissues) are very low.
2 Extracorporeal elimination techniques have been used world-wide in paraquat poisoning. Do they remove paraquat effectively? Certainly. Do they increase the survival rate? Probably not. The reason being that when these techniques of elimination are initiated, potentially lethal concentrations of paraquat have already been attained in the highly vascular tissues of vital organs and in pneumocytes.
3 The data presented here suggest that the successful treatment of paraquat poisoning will not be achieved by modification of toxicokinetics.

Introduction

The mortality from paraquat poisoning in man has been reported as being 30% (Proudfoot *et al.*, 1979). Between 1979 and 1985, we analysed blood and urine samples from 92 documented cases of paraquat poisoning. The mortality in these patients was 80%: 34 deaths were early and occurred as a result of vascular collapse; 40 deaths were delayed and were due to pulmonary fibrosis and/or sepsis.

The present paper summarizes our data and that of others on the toxicokinetics of paraquat and the modifications that may be achieved by extracorporeal methods of elimination.

Disposition of paraquat

For the purpose of discussion, the disposition of a drug may be regarded as for those processes that occur subsequent to absorption, namely distribution and elimination.

Distribution

The kinetics of paraquat appear to be similar in man and dog (Davies *et al.*, 1977; Hawksworth *et al.*, 1981). In the latter species, the plasma concentration–time curve shows a tri-exponential decline, suggesting a three-compartment model. (1) Blood is assumed to be the central compartment. The concentrations found in plasma and erythrocytes are approximately the same at least in the rat (Sharpe *et al.*, 1972); paraquat is not bound to plasma proteins (Lock, 1979). (2) The second or superficial peripheral compartment is thought to be composed of highly vascular tissues such as the kidneys, liver, heart, etc. Rapid exchanges occur between this compartment and blood. The anatomy and physiology of the lung suggest that this too is a highly vascular tissue, which will therefore be exposed early to any paraquat circulating in blood. (3) The third compartment lies within the lungs, especially the pneumocytes whose exchanges with the central compartment are slow (Hawksworth *et al.*, 1981). Paraquat is accumulated actively into pneumocytes through the polyamines transport system (Smith, 1982). It should be emphasized that although this is a slow process from the pharmacological point of view, it is rapid from the point of view of the clinician: lethal concentrations of paraquat may be achieved in the lung within 6 h of ingestion of 35 mg/kg. Patients are only rarely admitted to a hospital experienced in the treatment of paraquat poisoning within this period.

Peak concentrations of paraquat in the lung are reached 4–5 h after intravenous administration, and 5–7 h after ingestion, provided that renal function is normal. In the presence of renal failure (which normally occurs when more than 20 mg of paraquat/

kg have been ingested), the peak pulmonary concentration is not achieved for 15–20 h, or even later, and may reach very high values; impairment of renal function by as little as 5% produces a fivefold higher concentration of the herbicide in the lung. It appears that toxic concentrations in the lung may only be achieved in the presence of renal failure, as hypothesized by Hawksworth *et al.* (1981), although this does not occur if the pulmonary circulation is excluded from the blood compartment at an early stage. Theoretically, early exclusion of the pulmonary circulation would prevent accumulation of paraquat in pneumocytes. If it was practicable this procedure could possibly decrease delayed deaths from pulmonary fibrosis it could not prevent early deaths from vascular collapse.

Metabolism

Paraquat is not metabolized but is reduced to an unstable free radical which is then re-oxidized to produce a superoxide radical. The reduction of paraquat is associated with oxidation of NADPH. The toxicity of the herbicide is due both to the production of reactive oxygen species and to NADPH depletion. Paraquat is excreted unchanged in the urine (Murray & Gibson, 1974).

Elimination

Excretion of paraquat is almost exclusively renal; biliary excretion is very small (Daniel & Cage, 1966; Hughes *et al.*, 1973; Van Dijk *et al.*, 1975). Paraquat renal clearance is higher than creatinine clearance (Davies *et al.*, 1977; Lock, 1979; Purser & Rose, 1979; Hawksworth *et al.*, 1981; Bismuth *et al.*, 1982; Webb, 1983) and it may exceed 200 ml/min when renal function is normal. Huge concentrations (> 1 g/l) and large amounts of herbicide are excreted within the first few hours after ingestion of an overdose (Scherrmann *et al.*, 1983). The high renal clearance shows that paraquat is secreted actively by the renal tubules. Tubular secretion is inhibited completely by *N*-methylnicotinamide suggesting that paraquat is secreted through an active transport process that exists for bases (Davies *et al.*, 1977; Lock, 1979). After *N*-methylnicotinamide administration paraquat clearance approximates to creatinine clearance; hence, tubular back-diffusion is small (Davies *et al.*, 1977).

When renal function is normal, most of an ingested dose of herbicide is eliminated within 24 h (Hawksworth *et al.*, 1981). However, one of the first toxic effects of paraquat is to cause renal tubular necrosis which dramatically reduces the renal excretion of the compound ($t_{½}$ > 120 h) so it then occurs over as long a period as 10–20 days, allowing retrospective diagnosis of poisoning and determination of prognosis. The normal ability of the kidney to handle paraquat is so remarkable that toxic pulmonary concentrations can only be achieved if there is concomitant renal failure (Hawksworth *et al.*, 1981). This fact explains why the presence of renal failure is one of the peripheral determinants of a poor prognosis in paraquat poisoning. In our experience, 19 of 20 such patients died.

Methods to increase paraquat elimination

Forced diuresis does not increase renal excretion of paraquat because tubular reabsorption is small. However, its importance lies in the fact that it will maintain both glomerular filtration and tubular secretion, the kidneys being the main route of elimination of the herbicide.

Patients poisoned with paraquat are always dehydrated to some extent (Webb & Leopod, 1983; Williams *et al.*, 1984) because of gastrointestinal fluid losses; paraquat may also cause peripheral vasodilatation (Webb & Leopold, 1983). For these reasons, in the early stages of renal failure there is a functional component.

This functional impairment does not necessarily indicate a poor prognosis (Bismuth *et al.*, 1982) and should be corrected promptly to allow maximum elimination of paraquat before renal tubular necrosis develops (Lock & Ishmael, 1979). Volume expansion may therefore be required. The administration of free superoxide dismutase (SOD) could protect the renal tubules and is presently under evaluation (together with liposomal SOD and glutathione peroxidase) in our department. Frusemide can be given to increase urinary flow and to protect against tubular necrosis. However, in our experience, it does not modify the prognosis of paraquat poisoning (Bismuth *et al.*, 1982).

Peritoneal dialysis

Peritoneal dialysis is a poor means of removing paraquat (Fisher *et al.*, 1971; Carson, 1972). Indeed, this technique is only able to eliminate small quantities of the herbicide when plasma concentrations are very high.

Haemodialysis

The clearance achieved by haemodialysis (HD) is good when paraquat plasma concentrations are high (> 10 mg/l) and it can reach 150 ml/min (Okonek *et al.* 1982–1983; Van de Vyver *et al.*, 1983). However, clearance drops remarkably when the plasma concentration is less than 1 mg/l.

Haemoperfusion

Haemoperfusion (HP) is the most effective means of achieving extracorporeal elimination of paraquat

Table 1 Haemoperfusion in paraquat intoxication (60 mg/kg): identical clearance and various removals

Time (h)	*Serum paraquat at arterial inlet (A) (μg/l)*	*Serum paraquat at venous outlet (V) (μg/l)*	*Clearance* $\frac{A-V}{A}$ **Q (ml/min)*	*Paraquat removed (mg/h)*
10–11	1480	200	130	12
11–12	840	150	123	6
12–13	400	90	127	3
13–14	200	40	120	2
17	450	Versus second haemoperfusion		(Total = 23 mg)

*Q = blood flow = 150 ml/min

(Bismuth & Fournier, 1980). According to Okonek *et al.* (1982–1983), clearance achieved using Haemocol cartridges is more than 50 ml/min even when the plasma paraquat concentration is less than 0.2 mg/l. HD and HP can be used in series to increase total removal (De Groot, 1982; Van de Vyver *et al.*, 1983).

When the extracorporeal elimination system is effective (i.e. when paraquat levels in venous outlet approximates to zero), the plasma paraquat concentration drops dramatically within 1–3 h. As a result, the amount of herbicide removed at the end of the single session is low, even when the clearance is still good (Table 1) (Bismuth & Fournier, 1980). When the procedure is stopped, a rebound in plasma concentration is observed, necessitating a second period of HD and/or HP. Therefore, Okonek's proposal of 'continuous haemoperfusion' appears logical (Okonek *et al.*, 1979). He reported the survival of several patients treated with this technique whose initial paraquat plasma concentrations were above the borderline, according to the predictive curve of Proudfoot *et al.* (1979), as modified by Scherrmann *et al.* (1983). However, the results achieved by Okonek *et al.* (1979) have not been reproduced by other workers. In all large series, including ours, HP and/or HD do not improve the prognosis of paraquat poisoning when plasma concentrations are above the predictive curve. Moreover, there is a negative correlation between the amount of paraquat eliminated through HP–HD and the time of death: the larger the amount of paraquat removed from the blood, the greater the probability of early death (Figure 1). Survival is only observed when early plasma concentrations (and consequently the amount of paraquat removed) are low or undetectable. The following case provides an example (see Table 2). A 35-year-old man was admitted to our department 9 h after the ingestion of 15 g of paraquat. The plasma paraquat level was 46.5 mg/l at 5 h postingestion. HD and HP series were started at 11 h, by which time the plasma concentration had dropped spontaneously to 22 mg/l because of renal elimination and tissue uptake. As a result of HD–HP, the level decreased still further to 4.5 mg/l within 4 h. However, the patient died of cardiovascular collapse at 15 h postingestion of the overdose. The total amount of paraquat removed by HD–HP was 750 mg whereas 500 mg were eliminated in the urine between the second and fifteenth hour. During the HD–HP session the amount excreted through the kidney fell dramatically (though the paraquat renal clearance was maintained) because the plasma concentration was lowered.

In this case, it is obvious that despite the efficacy of both renal and extracorporeal elimination of paraquat, a lethal amount of the substance had already been taken up by vital organs before admission and this proved overwhelming. The clearances achieved by HP and/or HD can equal the renal clearance of paraquat, but the total amount removed remains

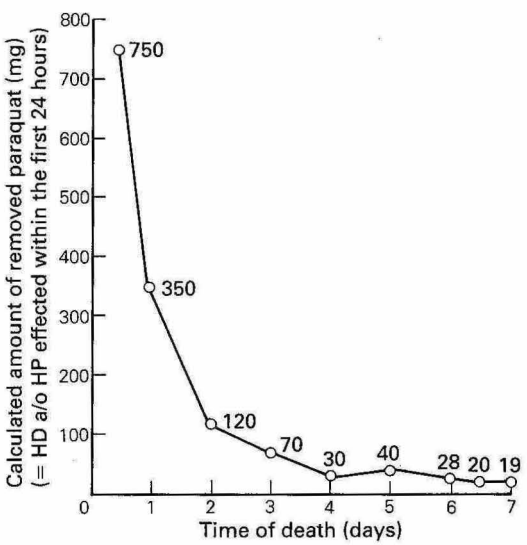

Figure 1 Efficiency of haemoperfusion (HP) and haemodialysis (HD)/time of death of patient

Table 2 Elimination of paraquat (15 g) through haemodialysis (HD) and haemoperfusion (HP) correlated with survival of patient

Time (hour no.)		*Plasma paraquat concn. (mg/l)*	*Removed paraquat (calculated) (mg)*
H5	Blood	46.5	
H11	Arterial	22	
	Post HD	15	234
	Post HP	2.5	
H12	Arterial	19	
	Post HD	7	204
	Post HP	4	
H13	Arterial	23	
	Post HD	10	228
	Post HP	4	
H14	Arterial	11.5	
	Post HD	6	84
	Post HP	4.5	
			(Total = 750)
H2	Urine (frusemide)		500
H15	H15		
	Death		

unchanged, unless renal failure occurs. These results suggest that the successful treatment of paraquat poisoning does not depend on modification of toxicokinetics (De Broe *et al.*, 1986). The peculiar disposition of paraquat limits the possible modes of therapy and explains the scepticism of experienced clinicians when confronted with apparently miraculous reports in the medical literature.

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Haemodialysis for Paraquat Poisoning

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1 Paraquat can be removed by haemodialysis and haemoperfusion but, although clearance values are high, the quantities recovered are insignificant. Prevention of death is most unlikely except perhaps in patients with plasma paraquat concentrations very close to the previously proposed line separating concentrations in fatal cases and survivors at different time intervals.
2 Even if delays incurred in measuring plasma paraquat concentrations and in setting up haemodialysis or haemoperfusion could be reduced to a minimum, elimination by these procedures would achieve little because paraquat disappears rapidly from the plasma in the first few hours after ingestion as it is taken up by the tissues and excreted into the urine.
3 Further studies on patients at borderline risk are required and the value of 'continuous' haemoperfusion requires further assessment.

Introduction

The distress and mortality caused by paraquat poisoning are such that, perhaps more than for any other poison, almost every conceivable form of treatment has been employed, often with several measures tried simultaneously, in desperate attempts to prevent death. Not surprisingly, haemodialysis and charcoal haemoperfusion have been used frequently both in the hope of enhancing removal of the poison and also in the management of paraquat-induced acute renal failure. Unfortunately, many early reports of survival after measures such as haemodialysis lack essential supporting laboratory evidence (Galloway & Petrie, 1972; Eliahou *et al.*, 1973; Thomas *et al.*, 1977). Moreover, at that time there was no way to determine prognosis and plasma paraquat concentrations could not be measured. Few hospital laboratories offer this analysis even today.

Paraquat poisoning has been managed at the Regional Poisoning Treatment Centre of the Royal Infirmary of Edinburgh since 1968 (Matthew *et al.*, 1968) and has gone through three phases in respect of the use of haemodialysis. Initially, and without more than theoretical considerations, it was thought that the procedure would be of no value and it was not used. However, increasing numbers of cases and a high mortality prompted a second phase during which virtually every patient was dialysed. Toward the end of this phase it became possible to measure paraquat concentrations and the many urine and plasma samples that had been stored were assayed retrospectively in an effort to assess the role of dialysis objectively. The results obtained had two important consequences. First, the plasma paraquat concentration related to the time from ingestion could be used as a prognostic indicator (Proudfoot *et al.*, 1979) and, secondly, as reported here, they showed clearly that haemodialysis was ineffective and led to the third and current phase in which it is again not used.

Patients and methods

Fifty-three adults (32 males and 21 females) in whom paraquat ingestion was confirmed by measurement of plasma paraquat concentrations or qualitative urine tests were studied. Twenty-three took formulations containing 20% (w/v) paraquat and 28 drank solutions of Weedol (2.5% w/w paraquat). One of the remaining two ingested a solution containing 8.8% (w/v) paraquat and the concentration in the other was never discovered.

Each patient was allocated to one of four groups in which the risk of death was considered high, borderline, low or uncertain depending on the proximity of his pretreatment plasma paraquat concentration to the prognostic line (Proudfoot *et al.*, 1979).

Most patients treated by haemodialysis were selected arbitrarily according to the amount of para-

Table 1 Risk groups according to the paraquat concentration of the formulation ingested

Risk group	*No. of patients*	*Paraquat concentration (%)*			
		20	*8.8*	*2.5*	*Not known*
High	16	13	—	3	—
Borderline	7	5	—	1	1
Low	29	4	1	24	—
Uncertain	1	1	—	—	—

quat ingested and the intensity of the blue colour developed when sodium dithionite was added to alkalinized plasma or urine. Only a small number of the later patients were selected because their plasma paraquat concentrations indicated a hopeless prognosis.

Plasma and urine paraquat dichloride concentrations were measured by a colorimetric technique (Jarvie & Stewart, 1979) which was shown to give comparable results to radioimmunoassay (Stewart *et al.*, 1979).

The amounts of paraquat removed by haemodialysis were calculated from the arteriovenous difference over the dialyser and the blood flow rate.

Results

Plasma paraquat concentrations

The plasma paraquat concentrations in 47 patients admitted within 25 h of ingestion and their allocation to risk groups are shown in Figure 1 together with one at borderline risk admitted at 35 h. Of the patients admitted after this time interval, three were clearly at high risk (plasma paraquat concentrations 0.63, 1.15 and 2.80 mg/l at 28, 57 and 45 h respectively). Paraquat could not be detected in the plasma of one of the two remaining patients admitted late (although the urine test was positive) and the other had a plasma concentration of 0.04 mg/l at 90 h; both were considered to be at low risk. The total number of patients in each risk group according to the paraquat concentration of the formulation ingested is shown in Table 1.

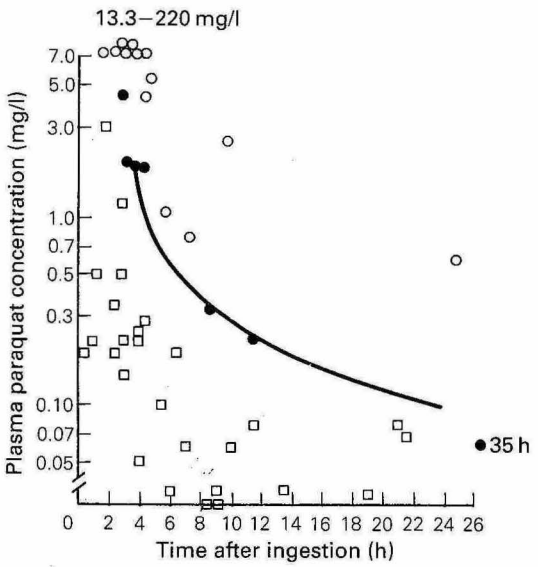

Figure 1 Plasma paraquat concentrations related to the time from ingestion in patients admitted within 26 h of ingestion and one at 35 h after ingestion. Patients at high risk (○), low risk (□) and borderline risk (●). The line is that of Proudfoot, A. T., Stewart, M. S., Levitt, T. & Widdop, B. (1979) *Lancet*, **ii**, 330–332

Twenty-six patients were dialysed, one (for technical reasons) with peritoneal dialysis alone, nine with haemodialysis alone and 16 with a combination of the two. The types of dialysis used according to risk are shown in Table 2.

Effect of dialysis on plasma paraquat concentrations

The typical effect of haemodialysis on plasma paraquat is shown in Figure 2. During each dialysis concentrations declined slightly only to rise rapidly again when the procedure was terminated, presumably due to shift of paraquat from the peripheral to the central compartment. Dialysis had no obvious effect on the final concentration of paraquat.

Table 2 Use of haemodialysis and peritoneal dialysis in different risk groups

Risk group	*No. in group*	*No. dialysed*	*Type of dialysis*		
			Haemo-	*Peritoneal*	*Both*
High	16	10	4	1	5
Borderline	7	3	2	0	1
Low	29	13	3	0	10
Uncertain	1	0	0	0	0

Table 3 Urinary and haemodialysis elimination of paraquat

Patient no.	Plasma paraquat concentration (mg/l)	Time after ingestion (h)	Urine		Haemodialysis	
			Paraquat content (mg)	Duration of collection (h)	Paraquat recovered (mg)	Duration (h)
1	1.91	0.5	21	12	4	8
2	4.75	4.3	106	26	3	8
3	2.63	10.0	112	14	9	6
4	44.50	2.5	1082	12	117	6

Table 4 Numbers of patients and deaths according to the paraquat concentration of the formulation ingested

Paraquat concentration in formulation (%)	No. of patients	No. of deaths (%)
20.0	23	15 (65)
8.8	1	0
2.5	28	1 (4)
Not known	1	1

Urinary and haemodialysis elimination of paraquat

The amounts of paraquat removed by haemodialysis and renal excretion in four patients with very different initial plasma paraquat concentrations are compared in Table 3. With one exception, the amounts recovered by dialysis over 6 or 8 h were negligible (3–9 mg). In the remaining patient 117 mg was eliminated by dialysis in 6 h but this was insignificant in the context of ingestion of many grams of paraquat and a plasma concentration of 44.5 mg/l 2.5 h after ingestion and 8.3 mg/l at the start of dialysis. In each case the mean rate of paraquat elimination in the urine exceeded that achieved by haemodialysis by a factor of 3.6–10.3.

Mortality

The mortality in relation to the formulation of paraquat ingested is given in Table 4. As expected, it was greatest (65%) in patients who ingested the 20% (w/v) concentrate and lower (4%) in those who drank solutions of Weedol.

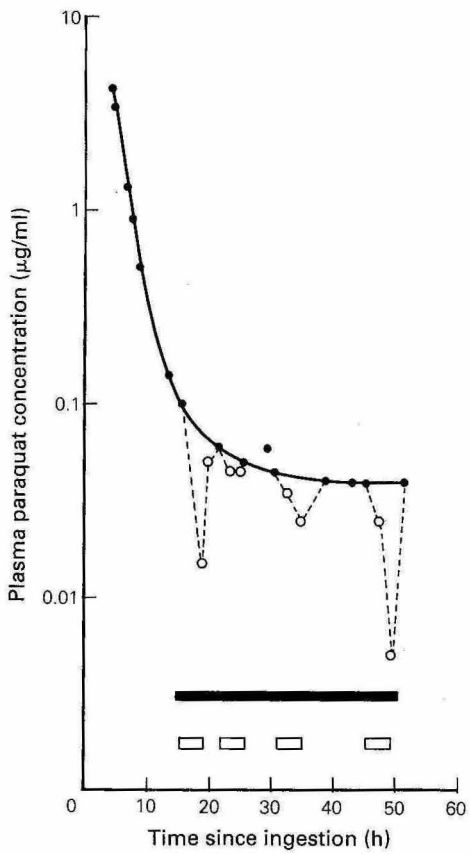

Figure 2 Serial plasma paraquat concentrations in a man aged 26 years who was treated by four 6-h periods of haemodialysis (□) during continuous peritoneal dialysis (■) and survived

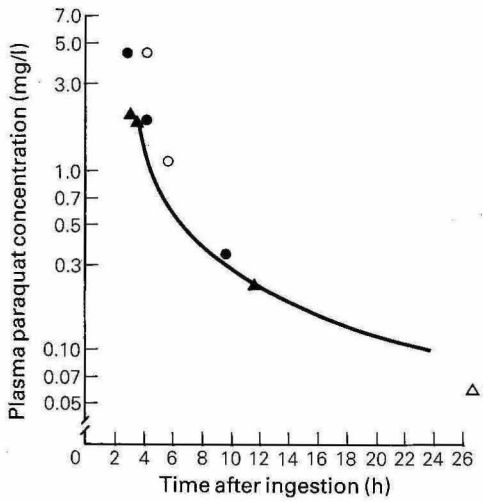

Figure 3 Plasma paraquat concentrations related to the time from ingestion in patients admitted within 26 h of ingestion and one at 35 h after ingestion. Patients at high risk, dialysed and survived (○), borderline risk, dialysed and survived (●), borderline risk, not dialysed and survived (△) and borderline risk, not dialysed and died (▲). The line is that of Proudfoot *et al.* (1979) (see the legend to Figure 1)

Table 5 Mortality and dialysis in different risk groups

Risk group	*Dialysed*		*Not dialysed*	
	No.	*Deaths*	*No.*	*Deaths*
High	10	8	6	6
Borderline	3	0	4	3
Low	13	0	16	0
Uncertain	0	0	1	0

Table 6 Ages and plasma paraquat concentrations of six men at high risk but not treated by dialysis

Age (years)	*Plasma paraquat concentration (mg/l)*	*Time after ingestion (h)*
65	220	3.5
76	120	3.0
31	15	2.0
64	0.80	7.5
47	0.60	25.0
49	0.63	28.0

Table 5 shows the mortality according to risk group and treatment by dialysis. Fourteen of the 16 patients (88%) in the high-risk group died, including eight of the 10 who were dialysed and all six men who were not. The plasma paraquat concentrations in all the latter cases (Table 6) were well above the prognostic line. The two patients who were dialysed and survived (the first of whom was patient no. 2, Table 3) had plasma concentrations of 4.75 and 1.07 mg/l at 4.3 and 6.0 h after ingestion respectively (Figure 3).

All 29 patients considered to be at low risk and the only one who could not be grouped with reasonable certainty survived; 13 of them underwent haemodialysis on one or more occasions.

Of the seven patients considered at borderline risk, three out of four not dialysed died while all three who were dialysed survived. The plasma paraquat concentrations are shown in Figure 3. Those who died (two men aged 70 and 29, and a woman aged 38 years) had paraquat concentrations of 1.95, 2.0 and 0.23 mg/l at 4.0, 3.5 and 11.75 h after ingestion respectively; the survivors had concentrations of 4.5, 1.87, 0.33 and 0.06 mg/l at 3.25, 4.3, 9.75 and 35.0 h respectively. Unfortunately, the number of patients in the groups was too small for statistical analysis.

Discussion

The present results confirm that very little paraquat can be removed by haemodialysis. During the procedure plasma paraquat concentrations decline faster than would be expected by endogenous elimination but, when dialysis is stopped, there is a rapid rebound (Figure 2) to levels which are probably little different from those that would have been expected without treatment. Paraquat is removed from the blood but the amount is an insignificant fraction of the total in the body because paraquat has a very large volume of distribution. The haemodialysis clearance of paraquat may be as much as 150 ml/min (Van de Vyver *et al.*, 1983) but, because plasma concentrations are usually low, very little is recovered. The amounts in our patients were similar to those reported by Spector *et al.* (1978) and Van Dijk *et al.* (1975). The greatest quantity (117 mg in patient no. 4, Table 3) was negligible in relation to the dose absorbed and a plasma concentration of 44.5 mg/l 2.5 h after ingestion. The very small fraction of the dose eliminated by dialysis could not be expected to influence the outcome and during the critical early stages the mean hourly excretion of paraquat by the kidneys is 3–10 times greater. The clearance of paraquat and the amounts removed by charcoal haemoperfusion are similar to those achieved by haemodialysis (Okonek *et al.*, 1982–1983; Van de Vyver *et al.*, 1983, 1985). Mascie-Taylor *et al.* (1983) recovered only 2.5–19.1 mg in five cases while Vale & Meredith (1981) removed a mean of 96.25 mg in 12 cases (range 8–280 mg).

Haemodialysis clearly is not indicated in patients with plasma paraquat concentrations below the prog-

nostic line who recover anyway and will not prevent the deaths of those well above it. It is only likely to be of value in patients at borderline risk. Its use could be rationalized if two problems could be overcome. The first is the rapid identification of those patients who are likely to die and who may therefore be suitable for treatment with elimination techniques. Clinical assessment based solely on the paraquat concentration of the formulation ingested, the quantity ingested and the qualitative urine test clearly is impossible and we dialysed no fewer than 13 out of 29 patients who were later shown to be at low risk (Table 2). The only objective method of assessing risk is measurement of the plasma paraquat concentration in relation to the time from ingestion. However, plasma paraquat assays are available in only a few centres and, even then, delay in obtaining the result is inevitable. The second problem is that once a patient has been selected for haemodialysis or haemoperfusion, even in the most efficient of hospitals, there is a further delay of at least 2 h before the procedure commences. We now know that in patients who present within the first few hours after ingestion, plasma paraquat concentrations decline extremely rapidly as the poison is distributed to tissues and excreted in the urine. With the delay in starting treatment therefore, plasma concentrations at the commencement of dialysis or haemoperfusion are often very low and the plasma/dialysate diffusion gradient and hence the quantity of paraquat removed are correspondingly reduced. This is well illustrated by patient no. 4 (Table 3) in whom the plasma paraquat concentration of 44.5 mg/l when admitted 2.5 h after ingestion had fallen to 8.3 mg/l by the time that dialysis was started.

Superficial examination of the outcome of poisoning in patients at high and borderline risk might seem to suggest that even the small amounts of paraquat removed by extracorporeal procedures sometimes contribute to survival. In the former group, two out of 10 patients at high risk and who were treated by haemodialysis survived while all six not dialysed died (Table 5). Similarly, all three borderline risk patients who were dialysed survived compared with only one out of four not so treated. However, the apparent benefit may be more a reflection of the difficulty in assessing prognosis from the plasma paraquat concentration in borderline cases than of the efficacy of removal of paraquat. The present prognostic line is, at best, only a guide and, although supported by the experience of Bismuth *et al.* (1982), substantial discrepancies have been reported (Okonek *et al.*, 1982–1983; Hoffman *et al.*, 1983). In the borderline patients in our study (Figure 3) the first estimate of the plasma paraquat concentration was obtained only 3–5 h after ingestion and during this period concentrations are falling very rapidly. An error in the time of ingestion of as little as 0.5 h could therefore have a profound effect on the proximity of the patient's results to the prognostic line and the interpretation of the result. This seems a more probable explanation for the outcome in the borderline cases than removal of such small amounts of paraquat by haemodialysis and, while it is impossible to dismiss the possibility of benefit completely, on balance we feel that it is highly improbable that haemodialysis could make the difference between life and death.

The major obstacle to accepting this judgement is that Okonek and his colleagues (1982–1983) have claimed that 'continuous' haemoperfusion, defined as 8 h haemoperfusion/day for 2–3 weeks, removes sufficient paraquat to prevent the development of lethal paraquat-induced lung damage in patients whose plasma concentrations related to time from ingestion otherwise indicate a fatal outcome. Unfortunately, these observations have not been reproduced. Further assessment of continuous haemoperfusion and other elimination techniques is required, particularly in borderline-risk patients, and it is also important to establish that results obtained by the analytical technique used by Okonek *et al.*, are comparable with those obtained by the different methods used in other centres. These problems must be solved urgently, for the sake not only for the victims of paraquat poisoning, but also for patients with severe renal disease whose treatment may be disrupted by demands for emergency haemodialysis.

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Paraquat lung: is there a role for radiotherapy?

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1 We have previously reported the clinical course of a patient poisoned with paraquat who was treated with whole lung irradiation and who survived severe pulmonary damage.
2 Four further cases are reported who were much more severely poisoned and who died despite early pulmonary irradiation.
3 There is no definite evidence that this or any other form of cytotoxic therapy can influence the course of paraquat lung. As there is no adequate laboratory model, further investigation of such therapy should be in the context of a prospective clinical trial. Treatment of only one lung would allow rapid identification of a therapeutic effect of irradiation.

Introduction

In 1984 we reported the clinical course of a patient poisoned with paraquat who was treated with lung irradiation and who survived severe pulmonary damage.[1] This paper outlines the rationale of such treatment and reviews the outcome in four cases similarly treated.

Pathogenesis of paraquat lung damage

Paraquat is actively taken up by human lung[2,3], and peak levels occur within a few hours.[4] Toxicity is thought to result from either lipid peroxidation or from a reduction in cellular $NADP^+$ levels.[5] Histological studies reveal two distinct phases of lung damage. Initially there is destruction of the alveolar epithelium with alveolar oedema and an inflamatory exudate. Subsequently profibroblasts infiltrate the alveolar spaces and then proliferate and mature into fibroblasts which produce a diffuse *intra-alveolar* fibrosis.[6,7] This is a distinctive histological picture, but the biphasic response resembles that seen in the adult respiratory distress syndrome (ARDS), and probably represents the response of the lung to a range of toxic insults.[8]

Radiation tolerance of the lung

Radiation itself is toxic in high doses and can cause pulmonary damage with a biphasic histological picture similar to that described above for paraquat. However, acute pneumonitis occurs after 2–6 months and the later stage of fibrosis develops only after 9 months in both man and animals.[9] These effects depend both on the X-ray dose and on volume of lung irradiated: for example, high-dose damage to a small portion of the lung is usually tolerated without symptoms. It is possible to administer whole lung irradiation safely if the X-ray dose is limited. Similar care is required in the use of cytotoxic drugs, steroids and particularly oxygen which is well known to be toxic to the lungs.[8]

The radiation tolerance of the whole lungs is well established because such treatment has been used in the management of lung metastases[10–12] and a safe dose of 22.5 Gy in 15 fractions established.[10] In young patients with no known metastases, but a high risk of developing them, a dose reduction to 19.5 Gy in 13 fractions was advised for elective whole lung irradiation[13] and a dose of 17.5 Gy in 10 fractions was used in a clinical trial[14]; no toxicity was reported in either series. These doses were all specified at the mid-point of the mediastinum and it is important to realise that because of increased transmission the radiation dose to the lungs would have been some 15% higher.[10,14,15]

The total dose of radiation which can be tolerated depends on the way in which it is fractionated – both the number and size of fractions and the overall treatment time are important.[16] There is now an extensive literature on the tolerance of the lungs to large single doses of X-rays following the use of whole- or hemi-body irradiation, either in preparation for marrow transplantation, or in the palliation of advanced metastatic disease.[9,15,17,18] The risk of radiation pneumonitis increases with dose rate, but for conventional treatment machines a true corrected lung dose of 8.2 Gy (approximately 7.1 Gy uncorrected) carries a 5% risk.[9,15]

In the paraquat case previously reported[1] different

fractionation regimens were used for the two lungs – both were estimated (using the formula of Wara *et al.*[19]) to be approximately two-thirds of the tolerance dose of 22.5 Gy in 15 fractions quoted above, so as to give a wide margin of safety. This was to allow for the fact that the lungs were already damaged, that paraquat is a radiosensitizer, and for any possible interactive toxicity. The patient's lung function was impaired on follow-up, but there were no symptoms. We conclude that whole lung irradiation can be administered safely to patients with paraquat lung and would now recommend a dose of 11.25 Gy (uncorrected) in 5 daily fractions: the therapeutic efficacy of such treatment remains to be established.

Results of treatment of paraquat lung

Table 1 gives details of 5 cases treated by whole lung irradiation. Case 1 has previously been reported in detail.[1] The patient had a plasma paraquat concentration of 0.08 mg/l at 36 h at which time the predictive value of the data of Proudfoot *et al.*[20] is limited, though the plasma level was consistent with a fatal outcome. It is impossible to predict this patient's prognosis without lung irradiation on the basis of paraquat levels alone, as few patients present so late.[20,21] Of more importance is the fact that his lung function had shown progressive deterioration to the point of requiring ventilation. He improved rapidly following a course of irradiation to the whole of both lungs.

The other 4 cases treated with lung irradiation all had high plasma paraquat levels, developed dyspnoea within 4 days and were treated with oxygen, which is known to exacerbate paraquat toxicity in animals.[22] They all died with respiratory failure, as well as hepatic and renal damage. However, 2 showed a transitory clinical and radiological improvement after irradiation, which might have been due to chance, but which does suggest that the course of the disease was influenced. Several other patients have received irradiation at centres throughout the world, but none has been reported in the literature and apparently none has survived.

Recovery from paraquat lung damage has been reported even in patients severely affected and offered no active therapy.[32] Table 2 gives details of 17 reported cases who survived despite clinical and radiological evidence of pulmonary damage. Most were not adequately documented with blood gases or plasma paraquat levels (because a rapid assay was not available). In 4 of the 5 in whom paraquat levels were obtained, the predicted chance of survival was greater than 90%. All but 3 of the patients developed symptoms and X-ray changes after a delay of at least a week and only 1 was reported as being so dyspnoeic as to require oxygen therapy: this patient was unusual in that he had administered the toxin both intravenously and orally.[35] It is clear that spontaneous recovery can occur, and that pulmonary oedema, pleural effusion and inhalational pneumonia are important differential diagnoses.[27,28,31,33] Addo & Poon-King[36] recently reported 72 patients treated with a combined regimen of dexamethasone, cyclophosphamide, forced diuresis, oral sorbents and vitamins B and C. Their data do not indicate a definite change in prognosis as assessed by plasma paraquat levels.[20] A controlled trial for those at risk has been advocated.[37]

Discussion

There is no good evidence that the course of paraquat lung injury can be influenced by cytotoxic agents, and the picture is further complicated by well-documented cases of recovery without active intervention (Table 2). Late fibrosis also occurs in ARDS and a wide range of agents have been suggested for its prevention and treatment: none has an established place in management.[8] Similarly, the role of cytotoxics and immunosuppressants (other than corticosteroids) in the management of interstitial pulmonary fibrosis remains to be established in randomized clinical trials.[38]

If the therapy of paraquat lung is to be investigated in the laboratory, then a reliable model needs to be established. High single doses of paraquat produce acute alveolitis, but the fibrotic reaction is more variable and is only reliably produced by repeated low doses given in the diet or by injection[7,39,40] and even then there is considerable inter-animal variation (Smith, personal communication).

A recent paper by Parkins and Fowler[41] described the effects of single intraperitoneal doses of paraquat on lung function in mice. Respiration rate was used to obtain dose-response curves, and proved to be a sensitive index of paraquat toxicity. Irradiation given as a single dose 3 days after the toxin did not reverse paraquat lung injury, but instead exacerbated the damage slightly. Before applying these findings to man it is important to look at the experimental model: if the mice survived 3 days, then they did not die during the course of the experiment. This is not the clinical syndrome which occurs in man. Further, no histological studies were performed to confirm that fibroblast proliferation was actually occurring at the time at which irradiation was performed, and it is likely that irradiation was applied during the acute pneumonitic phase. The observed interaction between paraquat and irradiation was not entirely unexpected as paraquat is a highly electron affinic radiosensitizer, and as both modalities inflict injury by the generation of free radicals. Due allowance was made for this possibility when whole lung irradiation was used

Table 1 Patients irradiated for paraquat lung

Sex/Age	*Amount ingested*	*Serum paraquat level (mg/l)*	*Prognosis (% survival*)*	*Symptoms*	*Chest X-ray changes*	*Arterial Oxygen* kP_a	*Oxygen therapy*	*Specific treatment*	*Comment*	*Centre*
M 29	3 g Weedol	0.08 at 36 h	?70	Severe dyspnoea	Day 4	4.6	No	Cyclophosphamide steroids, irradiation started day 9	Rapid improvement	Cardiff[1]
M 58	20 ml Gramoxone	0.8 at 4 days	< 10	Severe dyspnoea	Day 4	3.6 (on oxygen)	Yes	Iradiation 15 Gy in 5 fractions started day 5	Died on day 15 after transient improvement in blood gases and CXR	Cambridge
M 63	Accidental	Present in urine	—	Severe dyspnoea	Day 5	6.4 (on oxygen)	Yes ventilated	Irradiation 15 Gy in 10 fractions started day 5	No benefit, died a respiratory death on day 19	Hamilton Ontario
M 20	50 ml Gramoxone	0.98 at 7½ h	30	Severe dyspnoea	Day 4	8.5	Yes ventilated	Irradiation started day 5	Respiratory death despite early irradiation	RAF Holton[23]
M 18	10 ml Gramoxone	3.0 at 4 h	20	Severe dyspnoea	Day 4	3.2	Yes ventilated	Irradiation 13 Gy in 6 fractions started day 4	Transient improvement, respiratory death on day 14	Plymouth

* From Hart *et al.*[21]

Table 2 Reported survivors of paraquat lung

Sex/Age	*Amount ingested*	*Serum paraquat level (mg/l)*	*Prognosis (% survival*)*	*Symptoms*	*Chest X-ray changes*	*Arterial Oxygen* kP_a	*Oxygen therapy*	*Specific treatment*	*Comment*	*Reference*
M 34	Mouthful Gramoxone	Present in urine	—	Dry cough	Day 14	—	—	Forced diuresis	—	24
M 68	Mouthful Gramoxone	—	—	Not stated	Day 16	—	—	—	—	25
F 35	4 oz Gramoxone	Present in urine	—	Dyspnoea on exertion	Day 12	—	—	Cyclophosphamide and steroids	—	25
M 7	Mouthful Gramoxone	0.006 on day 2	?90	Not stated	Day 4	—	—	Cyclophosphamide and steroids	—	25
M 66	Mouthful Gramoxone	Present in urine	—	Dyspnoeic at rest, cyanosed	Day 2	6.7	No	Digitalis, antibiotics	—	26
M 49	1 oz Paraquat Dual	Present in urine	—	None	Day 12	12.8	No	Forced diuresis	Pleural effusions only	27
M 47	Mouthful Gramoxone	Present in urine	—	Cough and frothy sputum	Not stated	9.4	—	Forced diuresis and steroids	Pulmonary oedema	28
M 15	Mouthful Gramoxone	Present in urine	—	None	Day 13	10.7	—	Peritoneal dialysis and steroids	—	29
M 32	20 ml Gramoxone	None in urine	—	Dyspnoea at rest	Day 7	6.7	—	Azothiapine and aminobenzoate	—	30

M 27	2 sachets Weedol	0.12 at 3 h	> 90	Not stated	Day 5	–	No	–	–	31
M 27	Gramoxone	0.05 at 8 h	> 90	None	Clear	–	–	–	CO transfer factor fell to 64%	31
M 39	50 ml Gramoxone	0.133 at 6 days	?	Dyspnoeic	Not stated	–	No	None	Recovery despite FVC 1.5 l	32
M 11	10 ml Gramoxone	Present in urine	–	Dyspnoea at rest	Day 8	7.9	–	Forced diuresis, Imuran and Prednisolone	–	33
M 32	Mouthful Gramoxone	None in urine	–	None	Day 10	Normal	–	Steroids	Small pleural effusions only	33
M 56	20 ml Gramoxone	Present in urine	–	Dyspnoeic	Day 6	7.1	No	Forced diuresis	Recovered over two months	33
M 32	50 g Paraquat – diquat	0.016 at 3 h	> 90	Dyspnoea on exertion	Day 15	10.5	No	Steroids and Colchicine	Late decline reversed by therapy?	34
M 42	i.v. and oral Weedol	2.3 at 4 h	25	Dyspnoeic and cyanosed	Day 4	5.1	Yes	Haemoperfusion	Well at 2 months	35

* From Hart *et al.*[21]

clinically and late deterioration in lung function was not observed.[1] At present there is no established animal model in which to assess the effectiveness of treatment of delayed pulmonary fibrosis induced by paraquat poisoning.

In clinical practice the role of lung irradiation is uncertain and it should now only be used in the setting of prospective clinical studies. It will be important not to treat those who will recover anyway; similarly it is clear that lung irradiation will not save severely poisoned patients who develop multi-organ failure and early pulmonary distress consequent to acute alveolitis. Patients considered for treatment should therefore have survived for at least 4 days and should have shown a progressive decline in lung function to the point of requiring oxygen therapy, as documented by blood gases.[1] Such patients may have survived an episode of renal failure with or without treatment; their prognosis without further intervention is likely to be poor. In the absence of new laboratory data and a reliable animal model, lung irradiation has the advantage that it is a localized treatment, which can be used to determine whether or not cytotoxic therapy influences the course of paraquat lung damage. If only one lung is treated the patient can act as his own control. Progress could be monitored with serial chest X-rays and differential function tests of the two lungs, for example, using inhalation of DTPA to quantitate alveolar ventilation and diffusion on a regional basis.[42] An improvement on the treated side would be an indication to irradiate the other lung also. As a conventional clinical trial using survival as the endpoint would require 100 patients to have a 90% chance of demonstrating an improvement in survival from 30–60%[43], unilateral irradiation would permit a definite answer using the least number of patients. This is an important consideration in the United Kingdom where there are less than 40 deaths per year from paraquat poisoning (Office of Population Censuses and Surveys). Of these only 10 might be eligible and 5 studied per year. A standard clinical trial would be possible in Japan where there are 1400 deaths per year, but clearly new preventative measures are a more pressing need.

Conclusion

The role of lung irradiation remains in doubt: a dramatic case has been reported, but no confirmatory reports have followed. We suggest that useful responses will only be seen in those on the borderline for survival as defined by Proudfoot *et al.*[20] and that this hypothesis should be tested in prospective clinical studies. Those who have been severely poisoned and who have early pulmonary symptoms consequent to massive alveolar destruction cannot be expected to benefit from local irradiation to the lungs.

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Human Toxicol. (1987), **6**, 83–86

Emergency Analysis of Paraquat in Biological Fluids

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1 A variety of spectrophotometric, gas and liquid chromatographic and radioimmunoassay techniques have been applied to the measurement of paraquat in biological fluids. A brief review of these techniques is presented.
2 The majority of described methods are far from suitable in the provision of an accurate and reliable quantitative result in an emergency situation and the further development of suitable 'rapid' techniques is desirable.
3 The preparation and characterisation of internal accuracy control materials and the introduction of an external quality assessment scheme would be valuable in the improvement of laboratory investigations of paraquat poisoning.

Introduction

The rapid qualitative and quantitative analysis of paraquat in biological fluids is of undoubted value in both the initial assessment as well as the immediate prognosis of acutely poisoned patients. Quantitative measurements in plasma are of further value in the decision to use or withhold more vigorous forms of therapy, for example haemodialysis and haemoperfusion, and also to monitor their efficacy. On ingestion, the absorption of paraquat is extremely rapid, with peak plasma concentrations being obtained within 0.5–2 h, followed by an equally rapid decline in concentrations over the next 12–24 h.[1] A number of retrospective studies have demonstrated that a good prediction of outcome may be obtained from plasma and to some extent urine concentrations within the first 24 h of admission.[1–3] Whereas plasma paraquat concentrations in excess of 10 mg/l are invariably fatal, the possible prognosis for other patients may be less certain and will depend on the time interval between ingestion and measurement of plasma paraquat concentration (Figure 1). Urine paraquat concentrations of specimens taken on admission are also a reasonable guide to the severity of poisoning and have the advantage that a qualitative or semi-quantitative result may be easily and rapidly obtained in an emergency situation.[2,4]

A wide range of analytical techniques has been applied to the analysis of paraquat in biological fluids. Some of these techniques are more suited than others in their application to emergency analysis in cases of acute paraquat poisoning. The purpose of this short report is to review the application of the available analytical techniques to the problem of providing this service and the need for future analytical developments as an aid to the diagnosis and treatment of paraquat poisoning.

Qualitative test for paraquat

A simple qualitative 'spot test' for the presence of paraquat in urine, stomach aspirate and other concentrated fluids has been available for many years.[5,6] Its availability on an emergency basis for the rapid diagnosis of paraquat poisoning has also been strongly recommended.[4] The test is based on the reduction of paraquat by sodium dithionite under alkaline conditions to form its stable blue radical ion (λ max 603 nm). The related bipyridylium herbicide, diquat, also undergoes a similar reduction to form an analogous radical ion which is yellow-green (λ max 760 nm); the limit of detection of paraquat in urine or other clear fluids is approximately 1 mg/l and a negative result within 24 h of ingestion is a good indication that no significant quantity of paraquat has been ingested. A weakly positive, pale blue or blue-green colour generally indicates the ingestion of a small amount of paraquat or dilute formulations of mixed granules containing both paraquat and diquat such as Weedol. A strong 'royal blue' or 'blue-black' colour is generally a good indication of significant paraquat ingestion and a subsequent poor prognosis.[2] However, when this test is carried out, which particularly applies to 'on-call' situations, it is most important to ensure that both negative and positive controls are analysed

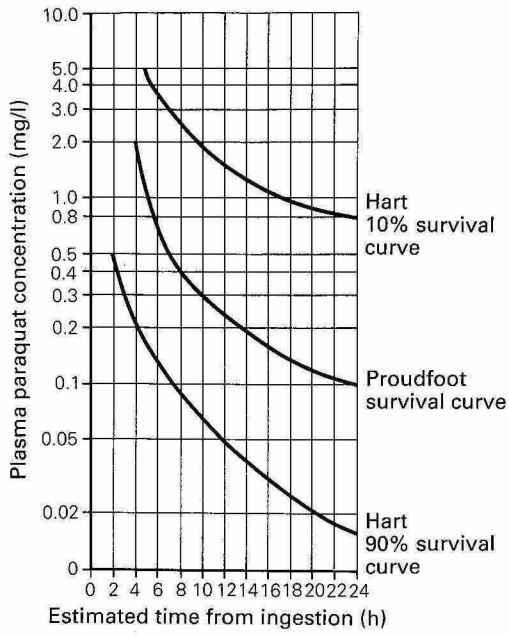

Figure 1 Relationship between plasma paraquat concentration and survival adapted from Hart *et al.* (1984)[3] and Proudfoot *et al.* (1979).[1]

with each patient specimen. Failure of the test is almost invariably due to the use of sodium dithionite which has oxidised on storage. Moreover, this reagent may not be readily available in some laboratories, although special formulation in gelatin capsules, as suggested by Widdop[7] can overcome this problem.

Quantitative analysis of paraquat

Spectrophotometric methods

The earliest spectrophotometric methods for the qualitative determination of paraquat in biological fluids (mainly urine, faeces and dialysate) that were reported[5,6,8] were based on extensive previous work on the determination of paraquat in food crops as described by Calderbank & Yuen (1965).[9] These methods are based on the initial isolation and concentration of paraquat (and diquat) from solutions or digests by cation exchange chromatography followed by acid clean up and elution with ammonium chloride. The concentrated eluate is then reacted with alkaline sodium dithionite solution to produce the stable radical ion of paraquat which can be determined at 602–625 nm[5,8] or the more sensitive lower wavelengths of 392–401 nm as described by Berry & Grove.[6]

A simplified spectrophotometric technique for the rapid analysis of paraquat in plasma was first described by Knepil.[10] This technique reported a lower limit of detection of 0.1 mg/l for paraquat using a 2 ml volume of plasma and was the first method that could be applied to the rapid measurement of plasma paraquat concentration in cases of serious overdosage (Knepil).[11] Subsequent spectrophotometric methods have attempted to improve the limit of detection for the measurement of paraquat in plasma and to limit interference from the presence of diquat or various endogenous substances. This has been successfully achieved but only at the expense of speed and complexity of the analytical manipulations required.[12,13] These methods rely on the extraction of paraquat from plasma using an ion-pairing technique with sodium dodecyl sulphate, followed by back extraction into saturated salt solution prior to reaction with alkaline sodium dithionite. This requires a scrupulous attention to detail, particularly the use of cleaned glassware, high purity reagents and careful transfer of organic phases. Quantification of the final product is carried out by direct spectrophotometry as described by Jarvie & Stewart[12] or a later refinement of the original technique using electronic second and fourth derivative spectroscopy as described by Fell *et al.*[13] These later methods although suitable for research purposes are not an ideal choice for providing a rapid and reliable result on an emergency basis.

Gas chromatography

The earliest chromatographic method for the determination of paraquat in biological fluids was applied to its rapid analysis in urine.[14] This method was based on the pyrolysis of paraquat in the injection port of the chromatograph to produce a 4-4′dipyridyl product which was measured by flame ionisation detection with a limit of detection of approximately 0.1 mg/l in urine. This same technique was later extended to the analysis of paraquat at much lower concentrations in plasma and urine with the use of nitrogen selective detection or mass fragmentography.[15] An alternative approach to paraquat analysis based on its reduction in aqueous alkaline solution with sodium borohydride to form a hexahydro (diene) derivative that is then isolated by solvent extraction was described by Draffen *et al.*[16] and Van Dijk *et al.*[17] Quantification of the resulting diene was carried out by gas chromatography and either flame-ionisation, nitrogen selective or mass fragmentographic detection depending on the required sensitivity. All of the reported gas chromatographic techniques are generally only suitable for research purposes and not amenable to the rapid analysis of emergency specimens. Moreover, mass spectrometric analysis is not widely available in clinical centres.

Radioimmunoassay (RIA)

A specific radioimmunoassay procedure for the determination of paraquat at low concentrations in

both plasma and urine was first described by Levitt[18,19] and subsequently successfully applied to the 'rapid' determination of plasma paraquat concentrations in cases of poisoning.[19] This radioimmunoassay procedure was based on antibodies raised against a paraquat derivative of monoquat, in rabbits and used ^{3}H-labelled paraquat as the tracer and a dextran/charcoal separation technique. Radioactivity of separated unbound paraquat was determined by liquid scintillation counting. This assay requires only a very small sample volume (10–100 μl) and has a claimed limit of detection of 0.6 μg/l of paraquat ion in plasma or urine. Other related herbicides such as diquat and morfamquat are reported not to cross react with the paraquat antibody.[19]

Fatori & Hunter[20] also described two variants of a specific radioimmunoassay procedure employing an antibody raised to a paraquat-BSA antigen that was then covalently linked to a particulate solid support media for ease of separation of bound paraquat. The 'rapid' assay developed for clinical use employed ^{3}H-paraquat as the tracer whereas a more sensitive but considerably slower modification of the assay used ^{125}I-labelled paraquat.

Liquid chromatography

Early attempts at a suitable liquid chromatographic method for paraquat in biological fluids were disappointing due to poor efficiency and resulting low sensitivity.[21,22] Recently, however, more successful methods have been described although the application of high performance liquid chromatography (HPLC) techniques to clinical specimens has been somewhat limited. Gill *et al.*[23] have described a useful method for the determination of both paraquat and diquat in urine which shows a greatly improved efficiency. This method is based on the initial extraction of paraquat and diquat from urine using a Sep-Pak C_{18} cartridge, with ethyl viologen (1,1 diethyl-4,4′-bipyridinium salt) as an internal standard. Chromatography was carried out using an ODS-silica column and ion-pair separation with methanol and sodium heptanesulphonate as the mobile phase. The reported lower limit of detection for the determination of paraquat and diquat in urine was approximately 1 mg/l for both compounds. It is, however, unfortunate that the authors[23] did not apply this method to the determination of paraquat in serum at even lower concentrations. Interestingly, Querée *et al.*[24] have recently reported an HPLC method for the determination of paraquat in liver and haemolysed blood which is based on the ion-pair solvent extraction of paraquat with sodium dodecyl sulphate prior to ion-pair reverse phase chromatography using a C_{18} Bondpack column and octane sulphonic acid/orthophosphoric acid/methanol mobile phase. The reported limit of detection for haemolysed blood was 50 μg/l.

Choice of paraquat assay

The choice of assay for the rapid quantitative determination of paraquat in plasma is limited to several factors, such as sensitivity, availability of equipment and clinical demand. Radioimmunoassay is by far the most sensitive and specific of all the assays so far described for paraquat. However, it is somewhat laborious to perform requiring a high degree of technical skill to carry it out reliably. Radioactive scintillation counting has become a less often used technique in routine clinical laboratories, and reliable equipment may not always be easily available, particularly in an emergency situation. In contrast, radioactive γ-counting is widely available in laboratories but the relatively short shelf life (< 3 months) of suitably labelled reagents precludes the use of this technique for infrequent use. Other techniques such as gas and liquid chromatography, are limited in sensitivity, require considerable skill in their operation and are not widely available outside specialised toxicology centres. The various spectrophotometric techniques described also have their limitations. The more sensitive methods that have been described are difficult and laborious to perform and generally not suited to infrequent use on an emergency basis. Simpler but more sensitive spectrophotometric techniques such as that described by Knepil[10] may be more suitable in an acute situation, but would be of limited value in the investigation of patients who present late with relatively low but potentially fatal plasma paraquat concentrations (Figure 1).

A recent (January 1986) survey of 17 laboratories (16 hospital and 1 industrial research) in Great Britain which provide an emergency service for the measurement of plasma paraquat concentrations gave the following findings.

All laboratories reported a marked reduction in requests received in 1985 compared with previous years and emergency quantitative assays were currently being provided by only 11 out of 17 laboratories, although retrospective analyses were available from a further 3 laboratories. All but one of the 17 laboratories continued to provide an emergency qualitative test for paraquat. Of the 14 laboratories providing quantitative assays, RIA using tritiated paraquat was the preferred technique for 9 laboratories; the remaining 5 laboratories used various spectrophotometric methods, although one of these was in the process of changing to RIA. Gas or liquid chromatographic techniques were not used by any laboratory. An additional problem expressed by most laboratories was the difficulty in providing a reliable analytical service 'out of hours' particularly in busy hospital pathology departments. This is perhaps compounded by the lack of a reliable procedure for internal accuracy control or external quality assessment of paraquat

assays. This situation surely casts doubt on the reliability of results that might be (and are) provided by laboratories in an emergency situation. How this may influence patient management is difficult to assess.

Recommendations

1 Wider use and availability of the qualitative 'spot' test for paraquat using a reliable procedure with positive and negative controls.
2 Development of more rapid and sensitive assays for the quantitative measurement of plasma paraquat concentrations. An appropriate technology could be based on new developments in fluoro and enzyme immunoassay.
3 The preparation and characterisation of internal accuracy control materials for plasma paraquat analysis. A sterile liquid material containing a minimum of 5 ml of human plasma spiked with paraquat at 3 different concentrations in the range approximately 0.05–2 mg/l would be particularly useful.
4 Reintroduction of an external quality assessment scheme for those laboratories within Europe which are involved in the investigation of paraquat poisoned patients.
5 Where new therapies are claimed to be effective in the treatment of paraquat poisoning, attention should be paid to the support of such claims with accurate and reliable plasma concentration data.

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Human Toxicol. (1987), **6**, 87–88

Epidemiology of Paraquat in Japan and a New Safe Formulation of Paraquat

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Epidemiology study

According to statistics published by the Japanese Ministry of Health and Welfare, more than 1900 people were killed by paraquat in 1985 and the number of deaths is increasing sharply (Figure 1). More than 97% of deaths due to pesticides 'other than organophosphates and carbamates' (International Classification of Diseases, Code 989.3) in Figure 1 are considered to be due to paraquat poisoning. Other causes include organochlorines, blasticidin and chloropicrin which are only rarely the cause of death. The addition of emetics and colouring agents to paraquat formulations has had no noticeable effect on mortality.

We have treated 131 patients with paraquat poisoning in our poison treatment centre in the past four years, only 39 patients survived (mortality rate 70%). Prevention of paraquat poisoning whether as a result of accidents, suicide or homicide is thus urgent in Japan as well as in other countries.

New safe formulation of paraquat

A novel non-swallowable formulation—Paraquat Water Dispersible Granule (WDR)—developed jointly by Tsukuba University and SDS Biotech K.K. is considered to be one of the promising tools for the prevention of paraquat poisoning.

Paraquat WDG contains a natural thickening agent which makes it more difficult to swallow. Even when a lethal dose of paraquat WDG is dissolved in a glass of water, milk, soft drink, wine, etc., a non-fluidizable mixture is formed. The formulation can also be made more disagreeable to take by adding a stenching agent.

Methods

The following study was conducted in order to examine the elution rate of paraquat dichloride from ingested gel when in contact with gastric or intestinal juices.

Paraquat WDG (6 g) was gelled with 35 ml of water, to this was added 100 ml of artificial gastric or intestinal juice (made according to the Japanese Pharmacopoeia). In the dynamic study, gelled paraquat granules and artificial gastric or intestinal juice were added to a 500 ml separating funnel and shaken at approx. 50 mm amplitude 30 times/min. Temperature was maintained at 37°C in the stationary study and ranged from 20–30°C in the dynamic study. Samples (10 ml for stationary study and 5 ml for dynamic study) were withdrawn for determination of paraquat concentrations at 0 min, 10 min, 30 min, 1 h, 3 h, 6 h and 24 h after the mixing of gelled paraquat and gastric or intestinal juice. Immediately after each sampling, an equal volume of gastric or intestinal juice was added. The change in concentration due to this sampling method was corrected by calculation.

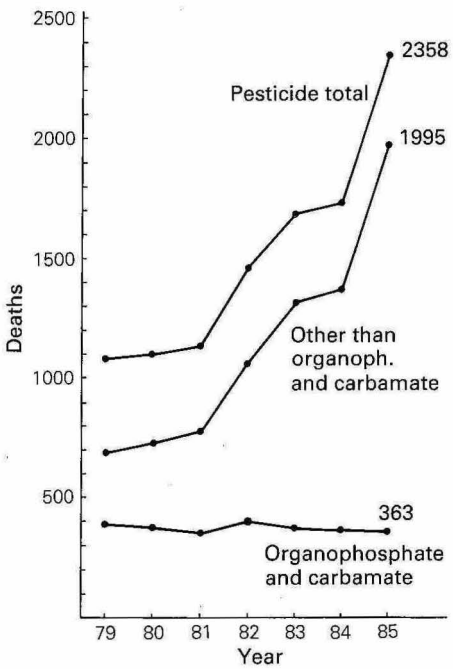

Figure 1 Number of deaths due to pesticide poisoning in Japan

The absorbance of samples was measured at 603 nm by Hitachi spectrophotometer Model 200-20 and the elution rate of paraquat dichloride was calculated using the following formula:

$$\text{Elution rate (\%)} = \frac{\text{Amount of paraquat dichloride in artificial gastric or intestinal juice}}{\text{Amount of paraquat dichloride in paraquat WDG}}$$

Results

The elution rate of paraquat dichloride from gelled paraquat into artificial gastric and intestinal juices is shown in Table 1 and Figure 2.

In the dynamic study, the elution rates reached only around 50% after 1 h. After that the elution rate was slow and finally reached 68.5% in gastric juice and 65.4% in intestinal juice at 24 h. The elution in the stationary study was slow compared with the dynamic study. This indicates that gelled paraquat, even if ingested, is much safer than liquid formulations. Paraquat WDG can easily be changed to an aqueous solution by diluting the composition with a large amount of water. The solution has low viscosity, is suitable for spraying, and shows the same efficacy as liquid paraquat on weeds.

Table 1 Elution rate of paraquat dichloride into artificial gastric and intestinal juices

	Elution rate (%)			
	Stationary study		*Dynamic study*	
Time	*Gastric juice*	*Intestinal juice*	*Gastric juice*	*Intestinal juice*
0	1.4	5.4	7.1	6.7
10 min	2.6	10.2	21.4	19.4
30 min	5.5	20.7	33.6	33.5
1 h	9.5	23.1	41.6	38.7
3 h	23.7	31.5	46.9	47.3
6 h	37.7	47.9	52.7	53.8
24 h	48.8	60.3	68.5	65.4

Conclusion

This is an important development. If further research can substantiate these observations and prove that the formulation is effective in its intended use, the WDG formulation could well result in a reduction in the number of fatal paraquat intoxications.

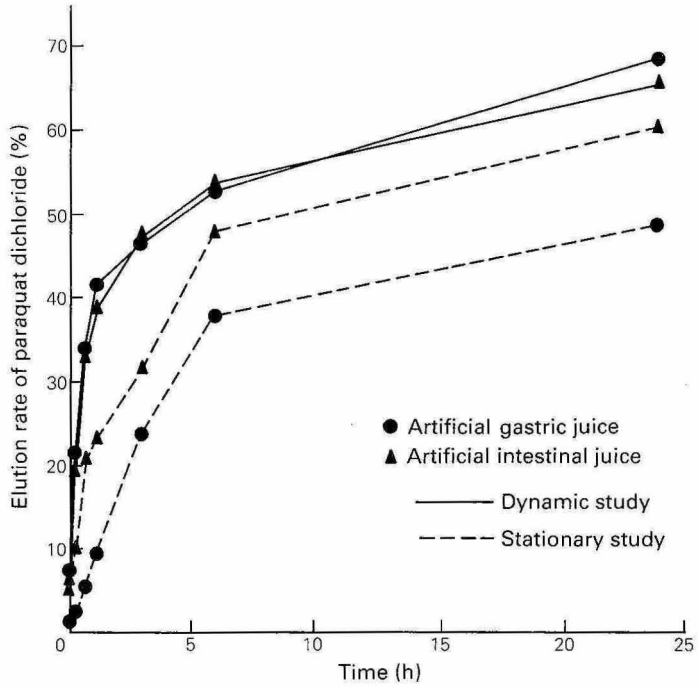

Figure 2 Elution rate of paraquat dichloride into artificial gastric and intestinal juices

Human Toxicol. (1987), **6**, 89–90

The Effectiveness of a Cation Resin (Kayexalate) as an Adsorbent of Paraquat: Experimental and Clinical Studies

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1 The cation-exchange-resin Kayexalate^{R} has an adsorption capacity for paraquat 15 times greater than activated charcoal and 6 times greater than Adsorbin. The oral LD_{50} of paraquat in rats rose 2.1 times by intragastric injection of Kayexalate.[1]

2 In the present study, the survival rate of rats given Kayexalate or Adsorbin after paraquat administration was examined. Results of clinical studies on 22 patients are also presented.

Animal study

Methods

Male Wistar strain rats weighing 170–360 g were used in this study. All animals were housed in facilities at a constant temperature of 20–23°C and relative humidity 40–60%. The dark-light cycle was 12 hours, food and water were provided *ad libitum*.

Results

Figure 1 shows the survival rate of rats given 0.5, 1 or 2 g/kg of Kayexalate or Adsorbin immediately after oral administration of 200 mg/kg of paraquat. 200 mg/kg of paraquat killed all animals not given an adsorbent within 3 days. Seven out of 8 animals given 2 g/kg of Kayexalate survived for more than 7 days whereas only 3 out of 8 animals given 2 g/kg of Adsorbin survived. However, when the dose of Kayexalate or Adsorbin was increased to 4 g/kg, survival rate after 7 days showed similar results in both groups.

To see the effect of length of time between paraquat administration and adsorbent administration, animals were given 2 g/kg of Kayexalate or Adsorbin 0, 0.5, 1, 2, 3 and 4 h after 200 mg/kg of paraquat

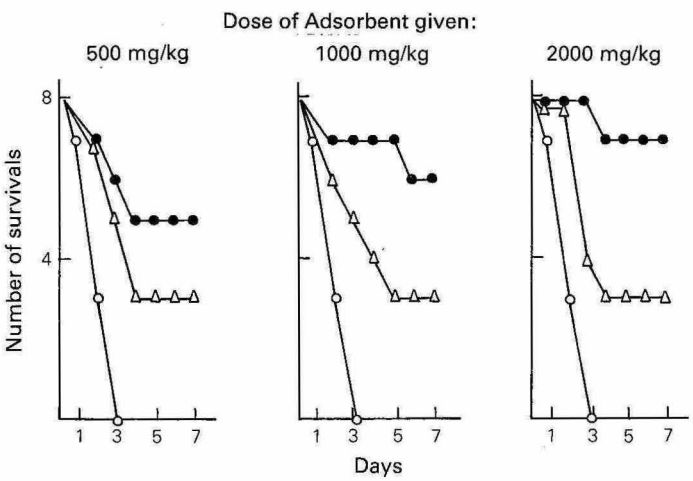

Figure 1 Alleviation of paraquat toxicity by adsorbents in rats. ○—○, paraquat; ●—●, paraquat + Kayexalate; △—△, paraquat + Adsorbin.

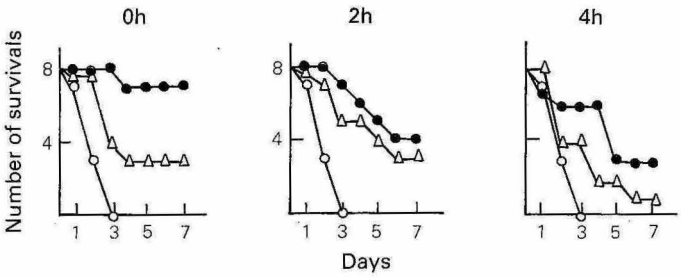

Figure 2 Alleviation of paraquat toxicity by adsorbents in rats. ○—○, paraquat; ●—●, paraquat + Kayexalate; △—△, paraquat + Adsorbin.

administration. Figure 2 shows the results of 0, 2 and 4 h after paraquat administration. Seven out of 8 animals survived for 7 days when Kayexalate was given immediately after paraquat administration. On the other hand, when Kayexalate was given 4 h after paraquat administration, only 3 out of 8 animals survived. Kayexalate administration even 4 h after paraquat administration showed an increased survival rate.

Clinical study

Methods

We also used Kayexalate on 22 patients with paraquat poisoning. The treatment protocol of paraquat poisoning is as follows: 100 g Kayexalate suspended in 1 l of normal saline is used for both gastric and intestinal lavage. 5–10 l of the suspension is used for gastric lavage. Since patients poisoned with paraquat vomit repeatedly, more than 10 l of fluid for lavage is rarely needed. A duodenal tube is then passed under X-ray examination into the duodenum. Intestinal lavage is carried out using 600–800 ml of the solution per h. Cathartics (magnesium sulphate, magnesium citrate or sorbitol) are given every 4 h. Catharsis could not be induced when the duodenal tube failed to pass the stomach because of severe vomiting.

Results

Six out of 22 patients survived. Although a control study comparing Kayexalate with Adsorbin has not yet been carried out, Table 1 clearly shows that when catharsis is effective, the chance of survival is high. On the other hand when catharsis is not effective, the mortality rate is high. This suggests that Kayexalate is effective in preventing absorption of paraquat from the gastrointestinal tract and can lower the mortality rate. However, in order to do this, Kayexalate should be distributed throughout the gastrointestinal tract. Further studies are needed including the measurement of plasma paraquat concentrations during Kayexalate therapy.

Table 1 Results of Kayexalate treatment

Catharsis and diarrhoea	*Survived*	*Died*
+	6	5
−	0	11

Chi-square test $P = 0.05$

Reference

[1] Takagi S, Yamashita M, Suga H & Naito H. The effectiveness of cation exchange resin as an Adsorbent of paraquat both *in vitro* and *in vivo*. *Veterinary and Human Toxicology* 1983; **25**: suppl. 1, 34–35.

Human Toxicol. (1987), **6**, 91–93

Prognostic Value of Plasma and Urine Paraquat Concentration

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1 A non-exponential mathematical equation was used to extrapolate the 'predictive line' for plasma paraquat concentrations beyond 24 h. Plasma paraquat concentrations were measured in 30 patients who were admitted more than 24 h after overdose. The extrapolated line accurately predicted the outcome in 27 of these 30 patients.
2 Urine paraquat concentrations were measured in 53 patients. All patients with urine paraquat concentrations of less than 1 mg/l (colourless or light blue test result using the colorimetric test) within 24 h of overdose survived. In contrast, patients with urine paraquat concentrations of more than 1 mg/l had a high probability of death.
3 Even if plasma paraquat concentrations have a higher predictive value, urine data may contribute to a more rapid evaluation of prognosis.

Introduction

Mortality from paraquat poisoning is high. Data have been reported which allow the prognosis to be predicted by measuring plasma paraquat concentrations during the 24 hours following intoxication.[1,3] The purpose of this paper is twofold. Firstly, to investigate the possibility of lengthening the 'predictive line' in order that prognosis may be determined in those patients who present later than 24 h after overdose. Secondly, to evaluate the relationship between urine paraquat concentrations and clinical prognosis. In addition, we have attempted to correlate the urine result obtained by a radioimmunoassay (RIA) technique with those given by the simple dithionite colorimetric test.

Patients and methods

Thirty patients were admitted to French intensive care units between 24 h and 12.5 days following intoxication (mean admission time 3.7 ± 2.7 days); they comprised 8 women and 22 men. Their ages ranged from 17–75 years. All patients ingested various amounts of paraquat except one patient who was intoxicated by percutaneous contact. Twenty-one patients died mainly from pulmonary fibrosis (mean time to death 11.25 ± 5.4 days).

Fifty-three patients admitted within 24 h of intoxication had a urine sample collected for the estimation of paraquat.

Plasma and urine paraquat concentrations were assayed by radioimmunoassay (RIA) whose reagents were provided by the Poisons Unit, New Cross Hospital, London.[4] Paraquat was also detected by the dithionite reaction. To 1 volume of the test urine was added 0.5 volume of freshly prepared 1 N NaOH solution containing 1% sodium dithionite. The blue colour produced is observed within the first minute.

Several mathematical equations were tested in order to simulate the 'predictive line'. A simple regression analysis was used to select the best fit by a Tektronix 4051 computer and the plot 50 statistics program [R] supplied by Tektronix (Beaverton, Oregon). The selected mathematical equations were used to extrapolate the 'predictive line' for several days. Each of the 30 plasma paraquat concentrations were plotted on a graph in order to correlate the prediction and the clinical data. In addition, kinetic studies performed in 2 patients were compared with the 'predictive line'.

Results

Two possible mathematical solutions were generated by regression analysis (Figure 1). The 'predictive line' is well fitted by a triexponential decay curve:

$$c = 319134\, e^{-1.43\,t} + 2794\, e^{-0.36\,t} + 489\, e^{-0.058\,t},$$

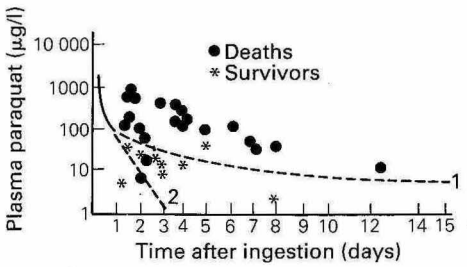

Figure 1 Plasma paraquat concentrations for 30 patients admitted after 24 h. The dashed lines represent the prolongation of Proudfoot's line using the hyperbolic equation (curve 1) and the triexponential equation (curve 2)

where c is the plasma paraquat concentration (µg/l) and t the time. This gives a terminal half-life of 11.8 h. In fact, this mathematical solution was not used because no satisfying correlation was found between dead and surviving patients admitted more than 24 h after poisoning. In contrast, a non-exponential solution was selected. The plasma paraquat concentrations, in µg/l, versus time, in h, are defined by the hyperbolic equation:

$$c = \frac{10^3}{0.471\,t - 1.302}$$

Table 1 indicates some specific paraquat levels up to day 15 obtained using this formula. Prognosis was accurately determined in 27 of the 30 patients (Figure 1). It can be seen that 2 plasma paraquat levels under the line were associated with a fatal outcome and 1 plasma level above the line was associated with survival. Surprisingly, one patient was admitted 12.5 days after ingestion with a significant plasma paraquat concentration of 20 µg/l.

Plasma paraquat concentrations generally ranged from 10–500 µg/l and remained at significant levels for several days. These data indicate that paraquat is eliminated slowly from the body and that the deep elimination phase reveals slow diffusion processes from tissues to peripheral fluids. These observations are confirmed by Figure 2 which shows 2 plasma paraquat kinetic profiles observed from the second and fourth days respectively until the patient's death. The kinetics demonstrate the slow disappearance of paraquat from the plasma and the parallel decline of plasma concentrations with the 'predictive line'.

Figure 3 summarizes the data observed by assaying 53 urine paraquat concentrations within 24 h of ingestion. Urine data were related semilogarithmically to time and showed a very wide range of concentrations from 1 µg/l–3300 mg/l. Plotted data were divided into patients who died very rapidly from cardiogenic shock (n = 14), patients who died later than 1 day from pulmonary fibrosis (n = 20) and survivors (n = 19). Moreover, the RIA paraquat urine levels were correlated to colours observed by the dithionite test; blue colours decreasing from dark blue to navy blue and light blue were observed. When concentrations less than 500 µg/l were present no colour was observed on the colorimetic test.

All the patients who died rapidly in less than 24 h showed urine paraquat levels of up to 10 mg/l. In contrast, when paraquat concentrations were less than 1 mg/l, all patients survived. However, 4 survivors exhibited urine paraquat concentrations above 1 mg/l. Patients who died from pulmonary fibrosis had urine paraquat levels between 1 and 1000 mg/l.

Table 1 Predictive plasma paraquat concentrations beyond 24 h separating surviving and non-surviving patients

Time (h)	*Plasma paraquat concentration (µg/l)*
24	100.0
48	46.9
72	30.7
96	22.8
120	18.1
144	15.0
168	12.9
192	11.2
216	10.0
240	9.0
264	8.1
288	7.4
312	6.9
336	6.4
360	5.9

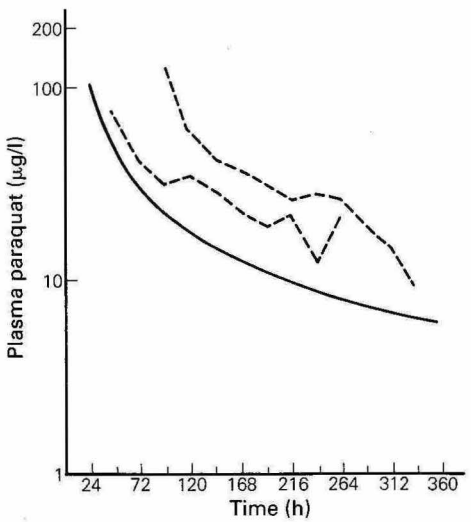

Figure 2 Two plasma paraquat kinetics issued from fatal cases (----) compared to the predictive line (——)

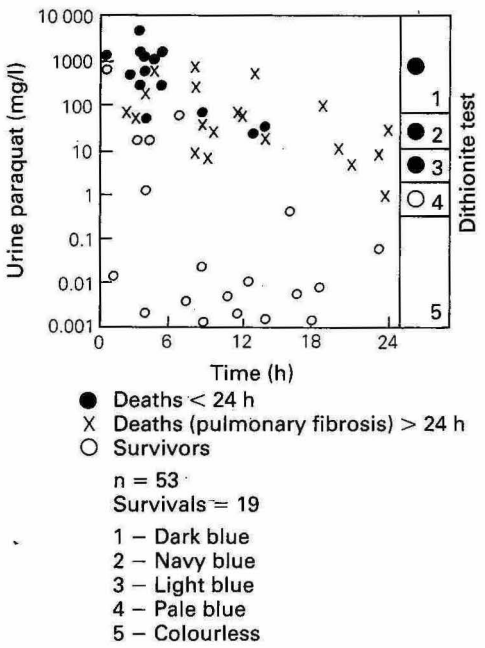

Figure 3 Evaluation of the predictive value of urine paraquat concentrations measured by radioimmunoassay and detected by dithionite test for 53 patients

Discussion

A 'predictive line' similar to the one described by Proudfoot *et al.*[1] which correlates plasma paraquat concentrations determined more than 24 h after intoxication would help clinicians considerably. It is for this reason that we tested different mathematical equations in order to extrapolate the 'predictive line' beyond 24 h. Our data permit us to extend the 'predictive line' up to several days. When comparing plasma paraquat concentrations with it, the predictive value was not absolute because it was only verified in 27 out of 30 patients. With a higher number of patients, the predictive value might be improved. Urine data confirmed the high extent of renal paraquat excretion.[5] The deep slope of the distribution phase observed with plasma data is associated with a high excretion rate of paraquat in urine as long as renal damage does not disturb the paraquat clearance. For this reason, urine paraquat concentrations were investigated in order to establish a clinical prognosis. Several basic limitations were apparent in the urinary study. Paraquat concentrations depend on the patient's diuresis. The duration of sampling is not always accurate and urine samples may be lost. Urine data are conventionally studied by determining the eliminated amount and the excretion rate of a compound. For both of these determinations the time interval of sampling and urine volume have to be accurately known. Despite these limitations, several conclusions can be drawn. Urine paraquat concentrations in the survivors' group were under 1 mg/l. Four survivors showed higher levels but the brief delay between ingestion and sampling in 3 of these (1, 3, and 4 h) may explain why high levels were found. All 4 patients had plasma paraquat levels in the survival area as defined by the line of Proudfoot *et al.*[1] The separation between survivors and non-survivors is not as obvious as for plasma data. However, when urine paraquat concentrations are above 1 mg/l the probability of death is high.

A comparison between RIA and dithionite test shows very interesting data. One aim of this study was to validate a rapid and simple analytical test to give a quick determination of prognosis. The dithionite test may be used in numerous laboratories and does not require sophisticated equipment as for RIA procedures. Moreover, this colorimetric test needs single reagents, 1 or 2 ml of urine and is not time-consuming. The examination of observed colours in comparison with prognosis and RIA values indicates that samples giving no colour or a very light blue colour come from patients who have a good prognosis. In contrast, blue colours are generally associated with a fatal prognosis.

Our data confirmed that by using a simple toxicological test for detecting paraquat in urine, it is possible to predict the prognosis with reasonable accuracy. Some overlap may appear but only when urine paraquat concentrations are above 1 mg/l. In this case, the clinical outcome is usually death. Plasma paraquat concentrations have a higher predictive value but the use of urine data may help clinicians to take therapeutic decisions more quickly.

We thank Dr J. A. Vale for his helpful criticism of the manuscript and his aid in translating the paper.

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Human Toxicol. (1987), **6**, 94–98

Evidence for Lipid Peroxidation in Man Following Paraquat Ingestion

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1 Four patients were investigated for evidence of lipid peroxidation between 4.5 and 36 h (mean 22 h) after ingestion of paraquat by measuring plasma phospholipid-2-esterified, diene-conjugated 18:2Δ9,11-linoleic acid (9,11-LA) and expressing it also as a ratio *R* (9,11-LA/9,12-LA × 100) of the 'parent' linoleic acid.
2 The mean value for *R* was 4.73 (range 3.7–7.1) at presentation and 6.91 at peak values (range 3.8–13.4) which occurred at a mean of 34 h after ingestion. Both values were significantly higher ($P < 0.001$) than that of 107 healthy controls (1.94, range 0.67–3.8).
3 Parallel changes in plasma vitamin E and 9,11-LA occurred in the 2 patients in whom serial measurements were made suggesting an involvement of vitamin E in the formation of this isomer.
4 These findings support the hypothesis that lipid peroxidation occurs during paraquat poisoning in man and the early appearance of 9,11-LA suggests that it may be a primary event.

Introduction

It has been postulated that pulmonary toxicity from paraquat is due to lipid peroxidation.[1] Paraquat undergoes cyclic reduction by microsomal NADPH cytochrome *c* reductase and reoxidation by molecular oxygen to generate the superoxide anion within the pulmonary epithelial cell.[2,3] Further metabolism to the more toxic hydroxyl radical may occur in the presence of transition metal ions.[4] However, although some experimental studies have shown that paraquat can stimulate lipid peroxidation through these mechanisms, others have failed to demonstrate such a process[5] and there is little information in man to support or refute this mechanism.

Conjugated lipid dienes have long been used as markers of lipid peroxidation *in vivo*, and recently the diene-conjugated non-peroxide isomer of linoleic acid (LA) has been shown to account for the majority of diene conjugation in human plasma.[6] In the present study we have measured plasma phospholipid-2-esterified diene-conjugated 18:2Δ9,11-LA (9,11-LA) in 4 patients with paraquat poisoning as a marker of lipid peroxidation *in vivo*.

Patients

Four patients (3 male and 1 female) mean age 35 years (range 25–45) were studied following ingestion of Gramoxone (20% w/v paraquat) (Table 1). The time interval from ingestion to presentation varied from 4.5–36 h. Paraquat ingestion was confirmed by a positive urine screening test in all cases and quantified by measuring plasma paraquat levels by radioimmunoassay.[7] In 2 patients (case 3 and 4) serial measurements of plasma paraquat were also performed. All patients received adsorbent therapy with either Fullers earth or activated charcoal. Three of the 4 patients died with fulminating respiratory failure (cases 1, 3 and 4) and all developed evidence of acute renal impairment; requiring peritoneal dialysis in case 3. Rises in serum aspartate aminotransferase indicative of hepatic damage occurred in all cases, though this was marked only in case 1, the most severely poisoned patient (Table 1). At no stage did the only surviving patient (case 2) develop either clinical or laboratory evidence of pulmonary dysfunction and 4 weeks following admission a chest radiograph showed no evidence of pulmonary fibrosis. At this time renal function had returned to normal.

Methods

Serial samples of plasma were aliquoted and stored at −20°C for measurement of phospholipid-2-esterified

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Table 1 Details of poisoning

	Case 1	*Case 2*	*Case 3*	*Case 4*
Age (years)	45	29	25	41
Sex	F	M	M	M
Time interval to presentation (h)	4.5	36	13	7
Initial plasma paraquat concentration (mg/l)	25	0.075	0.37	0.19
Treatment	Fullers earth	Fullers earth	Charcoal, renal dialysis	Charcoal, dexamethasone, cyclophosphamide
Organ damage	Pulmonary, renal	Renal	Pulmonary, renal	Pulmonary, renal
Peak plasma creatinine (μm/l) (normal < 115)	665	294	1135	767
Peak AST U/L (normal < 45)	395	62	59	52
Outcome	Death (45 h)	Survived	Death (10 d)	Death (90 h)

AST = Aspartate transaminase

18:2Δ9,11- and 18:2Δ9,12-linoleic acid (9,11-LA and 9,12-LA) using the method of Iverson *et al.*[8] This method employs phospholipase hydrolysis, solid phase sample preparation and reverse phase high performance liquid chromatography separation on a 5 μ silica C18 column (Hichrom). Two ultraviolet detectors (Laboratory Data Control) set at 234 nm and 205 nm in series were used to monitor the column eluate to detect 9,11- and 9,12-LA isomers respectively. Samples from the same patient were analysed in one batch. For each sample the LA isomer measurements (μmol/l) were used to calculate the percentage ratio *R*; (9,11-LA/9,12-LA × 100). The within-batch precision for *R* was less than 5% and the between-batch variation, performed on quality control material assayed on 10 occasions was 8%.

Vitamin E was measured by high performance liquid chromatography using a mobile phase of heptane: isopropanol, 99:1, with a 5 μ Lichrosorb Si 60 column after extracting 0.25 ml plasma into heptane. The column eluate was monitored on a Perkin Elmer LS-1 fluorimeter at 280 and 330 nm to detect vitamin E.[9] Calibration was performed using an external standard (DL α-tocopherol, Sigma). Within-batch and between-batch precision for this assay was 2% and 4% respectively and extraction efficiency > 95%.

Reference ranges for the different measurements were established using non-fasting plasma obtained from 107 randomly selected, healthy factory workers (62 male, 45 female, mean age 48.3 years) as part of a screening programme. The Student's *t*-test was used for statistical comparisons between patients and the control population.

Results

In all 4 patients initial and peak values for *R* (9,11-LA/9,12-LA × 100) exceeded the upper limit of normal established from our reference population (Table 2). In addition values of *R* were evaluated as early as 7 h after ingestion of paraquat (case 4). The mean of peak 9,11-LA concentrations for each patient was significantly higher than the reference mean ($P < 0.001$, Table 2) though the mean for initial concentrations was not. In contrast the mean initial concentration of 9,12-LA was lower than the value for the control population ($P < 0.01$) and was also significantly lower in the samples in which peak 9,11-LA levels were measured ($P < 0.01$).

Serial values of *R* for cases 1, 2 and 4 remained abnormal until either death or discharge (Figure 1). In case 3 a continuous fall in *R* occurred until death despite evidence of both pulmonary and renal damage. Similar changes occurred in absolute concentrations of 9,11-LA (Figure 2). In case 4 the concentration of 9,11-LA fluctuated markedly and on several occasions was above the reference range (55.8 μmol/l: mean + 2 s.d.) for this fatty acid. Concentrations approaching the abnormal range also occurred preterminally in case 1 (54 μmol/l).

Serial measurements of plasma paraquat are plotted together with concentrations of 9,11-LA in Figures 3 and 4. No clear relationship between paraquat concentration and 9,11-LA is apparent.

In cases 2 and 3, plasma vitamin E was also measured (Figure 2). In case 2, *R* remained essentially constant and a slight reduction in plasma vitamin E occurred. In contrast, in case 3, plasma vitamin E fell by 50%

over the period of observation and was below the normal threshold (11.6 μmol/l) from 40 h onwards. In both cases the plasma concentration of 9,11-LA closely mirrored that of vitamin E.

Discussion

18:2Δ9,11-LA accounts for 95% of plasma diene-conjugated lipids and has been proposed as a marker of lipid peroxidation *in vivo* since it can be formed from 18:2Δ9,12-LA by free radical generating processes in the presence of protein.[10] The finding of an elevated ratio in this study supports the hypothesis that lipid peroxidation takes place *in vivo* in man after paraquat ingestion. The reduced levels of 9,12-LA may represent a depletion of substrate through peroxidative mechanisms or a failure to incorporate 9,12-LA into phospholipids.

Evidence for a peroxidative process following paraquat poisoning in man is limited. Yasaka *et al.*[11] reported an elevation in serum malonaldehyde in a 20-year-old man who presented 4 days after paraquat ingestion with a combination of renal and hepatic failure. Levels of malonaldehyde remained abnormal for a further 11 days but were normal at the time of death.[11] Kurisaki[12] detected an increase in pulmonary and hepatic malonaldehyde measured in specimens taken from 7 cases of fatal paraquat intoxication immediately after death.[12]

However, in both studies evidence for lipid peroxidation was at a late stage in the patients' illness, suggesting that it might have occurred secondary to organ damage. The present study has produced evidence that this process takes place in the first few hours after paraquat ingestion, and is compatible with a primary role in the pathogenesis of organ damage.

Our findings throw no light on the organ(s) of origin of the 9-11-LA isomer though a pulmonary site would seem most likely since paraquat is accumulated in the lung by an energy-dependent mechanism. Concentrations of paraquat in the lung may reach levels that are up to 30 times higher than those of plasma.[13] Alternatively, sites such as the kidney and liver are possible since all of our cases developed renal and hepatic impairment. In support of a hepatic origin Brigelius *et al.*[14] found an increase in phospholipid diene conjugation in isolated perfused rat livers infused with paraquat.

Redox cycling of paraquat occurs at the expense of NADPH and results in a reduction in intracellular NADPH:NADP ratio. This would lead to a reduction in the level of cellular reduced glutathione and thus a decrease in the functional capacity of the primary antioxidant enzyme glutathione peroxidase. This sequence could render the cell more susceptible to peroxidative processes and Smith *et al.*[15] have

Table 2 Markers of lipid peroxidation following paraquat ingestion

	9,11-LA		*9,12-LA*		*9,11-LA/9,12-LA × 100*		*Time of sample*	
	Initial (μmol/l)	*Peak (μmol/l)*	*Initial (μmol/l)*	*Peak (μmol/l)*	*Initial (%)*	*Peak (%)*	*Initial (h)*	*Peak (h)*
Case 1	35.1	53.9	926	923.5	3.7	5.8	8	40
Case 2	39.2	46.6	982.2	1012.8	4.2	4.6	60	72
Case 3	33.5	33.5	876.7	876.7	3.8	3.8	13	13
Case 4	55	96.8	779.1	720.9	7.1	13.4	7	10
Mean (s.d.)	40.7 (8.5)	57.7 (23.7)	891 (74.6)	883.5 (106)	4.7 (1.4)	6.9 (3.8)	22 (22)	33.8 (25)
Control*								
Mean (s.d.)	30.9 (12.5)		1567.4 (4.55)		1.94 (0.64)			
(n = 107)								
P value								
(t-test)	n.s.	< 0.001	< 0.01	< 0.01	< 0.001	< 0.001		

* Reference population—factory workers

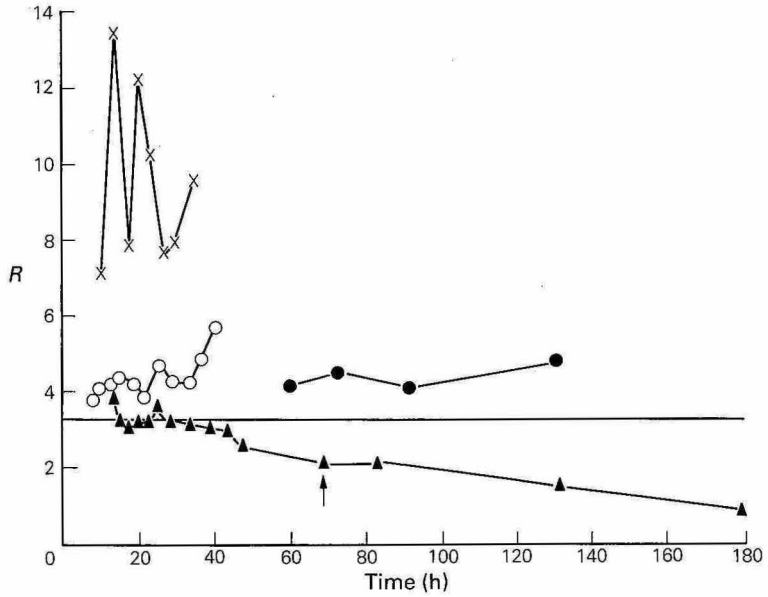

Figure 1 Serial measurements of plasma phospholipid-2-esterified, diene conjugated 18:2 Δ 9,11-linoleic acid (9,11-LA) expressed as a percentage *R*, of the parent 9,12-linoleic acid (9,12-LA), from 4 patients with paraquat poisoning. The horizontal line represents the upper limit of the reference range for the ratio *R*, i.e. 3.22% (mean + 2 s.d.). For case 3, the arrow represents the onset of peritoneal dialysis. Case details are given in Table 1

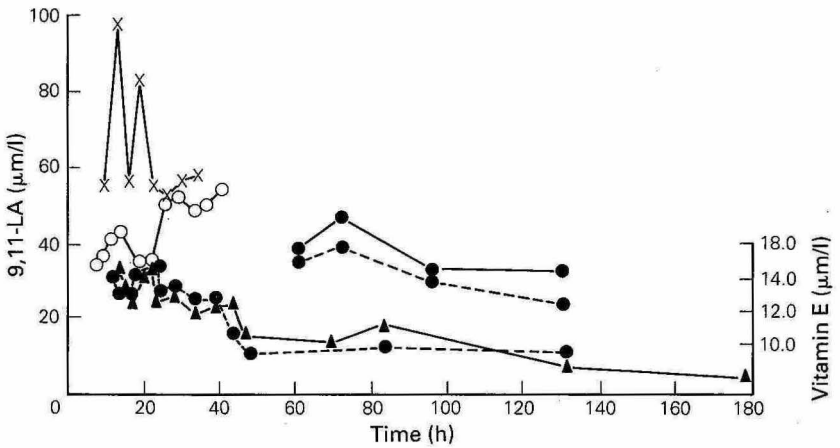

Figure 2 Serial measurements of plasma phospholipid-2-esterified diene conjugated, 18:2 Δ 9,11-linoleic acid (9,11-LA) from 4 patients following paraquat poisoning together with plasma vitamin E concentrations for 2 of the cases [● and ▲]. Plasma vitamin E concentrations are shown for case 2 (survival) and case 3 (death). Case details are given in Table 1. The upper limit for the reference range for 9,11-LA in healthy volunteers is 55.8 μmol/l (mean + 2 s.d.). For vitamin E the normal reference value was 11.6 μmol/l

suggested that such a process is the most likely one following paraquat poisoning. Alternatively the superoxide anion, which is generated by paraquat redox cycling may cause lipid peroxidation directly.[15] Our findings are compatible with either hypothesis.

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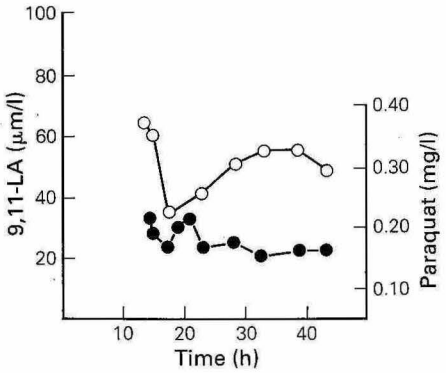

Figure 3 Serial measurements of plasma phospholipid-2-esterified diene conjugated, 18:2 Δ 9,11-linoleic acid (9,11-LA) [•] and plasma paraquat [○] in a fatal case of paraquat ingestion. Case details are given in Table 1 (case 3). The upper limit for the reference range for 9,11-LA in healthy volunteers was 55.8 μmol/l (mean + 2 s.d.)

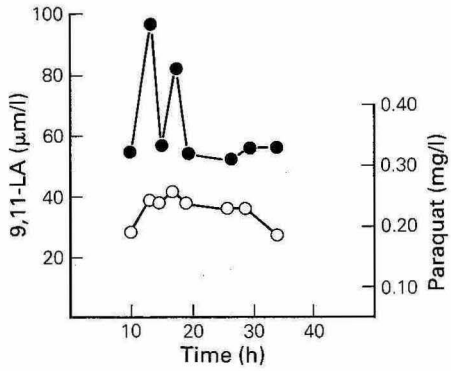

Figure 4 Serial measurements of plasma phospholipid-2-esterified diene conjugated, 18:2 Δ 9,11-linoleic acid (9,11-LA) [•] and plasma paraquat [○] in a fatal case of paraquat ingestion. Case details are given in Table 1 (case 4). The upper limit for the reference range for 9,11-LA in healthy volunteers was 55.8 μmol/l (mean + 2 s.d.)

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ABSTRACTS OF COMMUNICATIONS

Symposium

Paraquat Poisoning in Trinidad—A Report on 72 Patients with 52 Survivors

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Editorial note

A Poster was presented by Dr Addo detailing the treatment of 72 patients who had ingested liquid concentrates of paraquat. In addition to conventional measures, for example gastric lavage, fullers earth and activated charcoal, treatment included the use of high-dose cyclophosphamide and dexamethasone. The rationale behind the use of this treatment was to suppress the formation of superoxide anions by neutrophil leucocytes, which were postulated to be stimulated by paraquat.

A full paper giving details of this treatment regime has subsequently been published in The Lancet.[1]

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An Assessment of the Protective Effect of Cyclophosphamide and Dexamethasone in Rats

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Addo *et al.*[1] reported a treatment regime for human cases of paraquat poisoning that included the early administration of cyclophosphamide (CP) and dexamethasone (DX). They concluded that of the 20 patients poisoned 15 survived giving a 75% survival rate. Because of the absence of plasma paraquat values in these cases and the difficulty of establishing the effectiveness of a given treatment regime for paraquat poisoning in humans, we have studied the ability of CP and DX to protect rats from paraquat.

Thirty male rats were given 4 prophylactic doses of CP (2.5 mg kg^{-1}) and DX (0.15 mg kg^{-1}) at 12-hourly intervals. The rats were then given an approximate LD_{100} dose of paraquat (20 mg kg^{-1}) subcutaneously and the dosing with CP and DX continued for 6 days. All CP and DX treated rats survived whereas 20/22 rats given paraquat alone (20 mg kg^{-1}) died. However, when rats were given paraquat (20 mg kg^{-1}) followed by CP and DX no protection was evident.

There was approximately a 50% reduction in white cell count 48 h after commencing treatment with CP and DX. This decrease was largely due to a fall in the total number of lymphocytes. When rats were given CP and DX prophylactically for 48 h prior to dosing with ^{14}C paraquat, the retention of paraquat in the lungs of CP and DX treated rats was approximately 25% less (over a period of 24 h) than in the untreated animals.

It is therefore possible that the protective effect of prophylactic treatment with CP and DX against paraquat poisoning is related to either a depletion in white cell numbers (cf. Addo *et al.*[1]), or a reduction in the retention of paraquat in the lung or a combination of both. Preliminary studies show that by increasing the dose of paraquat by 25% no protection was obtained even with prophylactic treatment with CP and DX. Thus, for proper evaluation of the effectiveness of CP and DX treatment in cases of human poisoning it is important that the differential and absolute white cell count is followed during treatment. In addition, the plasma paraquat concentration should be measured, in order that an objective assessment of the likely outcome of poisoning can be determined prior to treatment.

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Human Myocardial Ultrastructural Changes following Acute Paraquat Poisoning—A Case Report

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Several morphological studies discussing the target organ toxicity of paraquat have been published but most have focused on damage to the lung parenchyma.[1,2] Myocardial involvement has been reported only rarely.[3]

A young 16-year-old female ingested about 3 g paraquat on an empty stomach. She was observed at a regional hospital and 5 h later was admitted to the intensive care unit. Gastric lavage was performed and Fuller's earth was given repeatedly and haemoperfusion was carried out daily for 5 d. Endoscopy showed a caustic oesophagitis and gastritis with superficial ulcerations. Plasma and urine paraquat concentrations were as follows:

	Plasma paraquat (μg/l)	*Urine paraquat (μg/l)*
Day 1	130	635
Day 2	0	3
Day 3	0	0.5

The patient developed progressive renal failure and there was blood gas and radiographic evidence of adult respiratory distress syndrome. On the 8th day after the overdose the patient died. At necropsy the following paraquat concentrations were found: liver 62.5 μg/100 g; lung, 78.1 μg/100 g; kidney, 125 μg/100 g.

Myocardial biopsy was carried out 15 min after death and electron microscopy showed non-specific changes including focal areas of partial or extensive lysis of myofibrils, Z band abnormalities, clusters of mitochondria which exhibited swollen forms and lysis of their cristie.[4]

Further studies will be necessary to clarify the effect of paraquat on the myocardial cells.

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Pulmonary Superoxide Dismutase Activity in Four Cases of Lethal Paraquat Poisoning

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The pulmonary damage of paraquat is believed to be mediated in part by a superoxide (SO) anion with a subsequent increase of lipid peroxidation. Paraquat lethality is enhanced by oxygen exposure and superoxide dismutase (SOD) inhibitors. SOD administration decreases paraquat stimulated lipid peroxidation.

In 4 cases of acute paraquat poisoning, lung specimens were removed immediately after death. Pulmonary cytosolic Cu SOD activity was measured by a colorimetric method using the reduction of nitroblue tetrazolium according to the method described by Fried.[1]

Lung histology showed alveolar oedema and vascular congestion in all cases, and a mild fibroblastic reaction in case 4. Lung SOD activity was strongly decreased: 2.04 ± 1.56 μg/mg of soluble protein. In post-mortem samples from humans without lung disease, the pulmonary SOD activity was 7.01 ± 2.17 μg/mg soluble protein.[2]

These results do not agree with experimental studies in the rat which show induction of SOD in the lung after exposure to non-lethal doses of paraquat.[3] Pulmonary SOD activity appears to be dependent on paraquat dose. At higher doses, paraquat may markedly decrease the SOD activity by inducing precocious and extensive lung cell damage.

A decrease of pulmonary SOD activity has also been reported in acute respiratory distress syndrome. Thus in paraquat poisoning, oxygen administration may potentiate lung damage by an increased generation of SO anion and also by a decrease of detoxification by SOD.

Case	Age	Time of death (h)	Lung (μg/mg soluble protein)		Paraquat concentration	
			Right	Left	Plasma (mg/l)	Lung (mg/kg)
1	23	18	0.66	3.16	1.21	7.25
2	55	12	2.54	2.66	3.9	
3	35	48	3.26	2.05		
4	23	132	0	–	1.28	0.25
Mean	34 ± 15.1	53 ± 54.9	1.61 ± 1.53	2.6 ± 0.55		

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Clinical Features and Pathological Findings in Two Cases of Paraquat Poisoning

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The clinical evolution of 2 cases of paraquat poisoning are presented.

Case 1: A 52-year-old woman was admitted shortly after the suicidal ingestion of 50 ml Gramoxone. She complained of burning in the mouth and throat. Physical examination was normal. The initial plasma paraquat concentration was 10 mg/l. Treatment was started immediately and consisted of gastric lavage, administration of Fuller's earth and cathartics, and charcoal haemoperfusion. Fuller's earth administration and haemoperfusion (3 h twice daily) were continued for 6 d. Despite this treatment and the administration of alphatocopherol (antioxidant agent) and acexamic acid (an inhibitor of collagen synthesis), the pulmonary compliance and CO_2 diffusing capacity decreased and the patient developed acute respiratory failure on the 6th day. She was intubated and initially treated with continuous positive airway pressure (CPAP) but continuous positive airway ventilation and an increased inspired fraction of oxygen (FiO_2) were rapidly required. She developed acute renal failure and hepatic necrosis and died 13 d after admission.

At necropsy the lungs were heavy and oedematous. Microscopically, the parenchyma was congested and most of the alveoli were filled with fibrinous exudate containing desquamated alveolar epithelial debris, red blood cells, some macrophages and lymphoid cells. Intra-alveolar fibroblastic proliferation was present and was associated in a few places with some interstitial fibrosis.

Case 2: A 25-year-old man was admitted with dyspnoea, hypoxemia and evidence of interstitial infiltration radiologically. He was an horticulturalist and had ingested granules containing 2.5% paraquat. Transient sore mouth and throat had been noted 14 d earlier. The patient was cyanotic. Analysis confirmed the presence of severe hypoxemia associated with renal failure and hepatic necrosis. Paraquat was detected in the urine. The clinical course was characterised by a rapid normalisation of renal and hepatic function, but severe respiratory failure supervened despite corticosteroid therapy and antioxidant agents. The possibility of a lung transplantation was considered but the patient died 15 d after admission (about one month after the poisoning) in irreversible hypoxemia.

At post-mortem the lungs showed diffuse fibrosis with areas of honeycombing containing cysts and subpleural bullae. Microscopically, the alveoli were filled with oedema and there was fibrin disposition. Some alveolar haemorrhages were observed. There was diffuse alveolar and interstitial fibrosis associated with the breakdown of the normal lung reticulin pattern. The inflammatory infiltrate consisted essentially of mononuclear cells. Some macrophages were present in the alveoli. Mucus was found in the bronchi. Foci of epithelial hyperplasia and glandular structures formed by pneumocytes were also observed near the bronchioles. The cysts and bullae were surrounded by fibrosis with destruction of the pulmonary architecture.

The microscopic findings in these 2 patients differ mainly in the extent and location of fibroblastic proliferation and fibrosis. Different stages of paraquat-induced lung damage could account for these various pathological findings which support the hypothesis of a primary alveolar epithelial injury in paraquat poisoning.

Eight Cases of Acute Paraquat Poisoning: Some Clinical Aspects

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Between 1972 and 1985, the clinical and toxicological aspects of 9 out of 19 cases of paraquat poisoning were studied in detail. One case was due to accidental ingestion: the other 8 were caused by voluntary ingestion. All 9 cases were admitted to the university hospital.

Of these 8 cases 6 were males. The patients were aged between 22 and 54 years. The approximate quantities swallowed were between 2 and 4 g in 6 cases and 10 and 20 g in each of the other 2. The time of admission after ingestion to a first hospital varied from 0.5 h–3 d. All patients, except one for whom no information was given, presented with vomiting. The time from ingestion to admission to the I.C.U. of the university hospital varied between 3 h and 10 d. Paraquat blood levels on admission varied between less than 0.1 and 19 mg/l. Paraquat concentrations were determined by a spectrophotometric method after separation on to ion exchange resin. Amongst the clinical signs, we noticed oropharyngeal inflammation or oesophagitis. The general therapy, in most cases, consisted of gastric lavage with activated charcoal, forced diuresis and haemoperfusion (6 HP in 1 case, 5 in 2 and 2 in 1), in order to completely eliminate paraquat from blood and urine with continuous monitoring of the levels. We administered bleomycin and corticosteroids in 6 cases. In another case we administered vitamins C and E as antioxidants.

We noticed a persistent metabolic (lactic) acidosis without shock in the 2 patients with the highest plasma paraquat levels (2 and 19 mg/l); the latter patient was fasting before ingestion. In addition, both patients rapidly developed oliguria and hypoxaemia before death. Significant increases of serum HBD, GOT, GPT and lipase activity were detected. A non-lactic acidosis was noticed in 2 cases where plasma paraquat levels were 0.3 and 0.8 mg/l respectively, 65 and 23 h after ingestion. These patients also developed oliguric renal failure but both survived even though moderate pulmonary fibrosis occurred in one case.

In one case where urinary retinol binding protein was studied, we noticed intermittent important increases of this protein denoting tubular dysfunction.

This study suggests that the presence of a persistent metabolic (lactic) acidosis (without shock) and oliguric renal failure refractory to therapy, may be important early prognostic features in addition to the quantitative determination of paraquat in the blood.

Survey of Enquiries about Paraquat Exposure Received at the Belgian Poison Centre from 1982–1985

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In Belgium, concentrated preparations of paraquat can be sold only by licensed dealers and their sale is restricted to professional users. However, paraquat is available to non-professionals in granular form up to a concentration of 2.5%.

We have reviewed the enquiries relating to paraquat received at the Belgian Poison Centre. About 20–30 cases are recorded annually and represent 1.2% of all pesticide enquiries. In the last 4 years we have received 101 calls; 94 related to adults. Exposure was accidental in 70 of these cases and 20 involved accidental ingestion. Seven children were involved, 3 of whom ingested paraquat accidentally. All 5 fatal cases recorded were suicides.

Paraquat Poisoning: A Report of Nine Cases

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Nine patients ingested paraquat with suicidal intent during the period 1980–1985. They were admitted to hospital between 1 h and 8 d after ingesting 50–500 ml of 20% paraquat (Gramoxone). The diagnosis was confirmed by qualitative analysis of blood and urine with sodium dithionite. For quantitative analysis gas–liquid chromatography was used (0.3–30.0 mg/l of paraquat in blood samples). The clinical picture was dominated by an elevated body temperature without an evident focus of infection, tongue and pharyngeal pseudomembranes, dyspnoea and cyanosis of central type, hypotension with tachycardia and cardiac enlargement accompanied by ECG signs of right ventricular strain, acute hepatic and renal failure with laboratory and clinical signs of defective haemostasis resulting in many cases of gastrointestinal haemorrhages.

Gastric lavage was undertaken and Bentonite or activated charcoal were given. Haemodialysis and/or charcoal haemoperfusion were performed and patients were ventilated mechanically with a low inspired oxygen and high nitrogen concentrations. In addition glucocorticoids, beta-blockers and tocopherol were administered. Despite these measures all patients died between 12 h and 17 d after ingestion. Two died due to irreversible ventricular fibrillation and 8 developed asystole after a short period of cardiogenic and toxic shock. Pulmonary fibrosis and oedema developed in 4 patients.

Autopsy showed cerebral oedema, prominent pseudomembranes of the tongue, pharynx and oesophagus, cardiac enlargement with myocardial necrosis, hepatomegaly with centrilobular necrosis, renal tubular and suprarenal cortical necrosis. Histological changes in the lungs showed destruction and desquamation of epithelial cells, oedema and hyaline membrane formation with infiltration and later fibroblast proliferation.

We suggest that paraquat be distributed only to approved users and in concentrations not greater than 5%. Centres with personnel trained in the management of paraquat poisoning should be established regionally.

Comparison of Paraquat and Diquat Intoxications

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Paraquat poisoning results in one of the highest mortality rates of all intoxications. In our patients there is a 90% mortality rate in suicidal cases and 50% in accidental cases. In 30 cases of paraquat intoxication we found the following characteristics: superficial ulceration of the mucous tissue of the mouth and oesophagus, mild reversible liver damage, and an acute reversible kidney failure. These features are followed by an irreversible fibrosis of the lungs which causes death. The patients are fully conscious until they die.

We have observed one case of diquat intoxication in which the patient ingested approximately 10 g of diquat. He developed multiple bleeding ulcers from the mouth to the duodenum. These lesions took 4 weeks to heal. Three days after the ingestion of diquat the patient developed acute kidney failure which had to be treated with 20 dialyses over 33 d. On day 5 after an improvement in the urea and creatinine concentrations, kidney function deteriorated again. The hepatotoxicity also showed a biphasic course. The first transaminase peak was found on day 5. On day 18 all liver function tests were normal whereas on day 23 there was a second peak of the liver enzymes in the blood. On day 2 the patient developed a very severe agitated organic psychosis which could only be controlled by long-term sedation and relaxation with artificial ventilation. Examination of the bone marrow on day 6 showed a pancytopaenia. By day 33 there was no improvement in the disturbed maturation of all 3 cell lines. No changes could be seen in lung function. Both intoxications were treated with the same therapeutic scheme: Bentonite, low O_2/high N_2-inhalation, gastrointestinal lavage, superoxide dismutase, artificial ventilation and continuous haemoperfusion–haemodialysis.

In one case of paraquat intoxication with kidney failure, paraquat could not be removed effectively by HP–HD because of its large volume of distribution (approximately 500 l). In contrast, it was possible to remove diquat from the plasma within 3 h of commencing HP–HD. The half-life of diquat was 75 min. Its concentration before treatment was 1.5 mg/l. Artificial ventilation can only prolong life in paraquat intoxications, whereas in diquat intoxication its long-term use led, in our case, to a complete recovery.

The Incidence of Paraquat Poisoning in an Epidemiological Study

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* On behalf of the Hospital Acute Poisoning Monitoring Group

With the support of the Acute Poisoning Monitoring Group, the incidence of paraquat poisoning or suspected poisoning has been recorded as part of an epidemiological study into acute poisoning as it presents at 21 Accident and Emergency (A&E) departments in England and Wales. This survey has been carried out over a period of 1 years, from 1st October 1984 and 7th January 1986, at each of these A&E departments.

The completed questionnaires contained information on the date and time of arrival at the A&E department, the age and sex of the patient, the agent(s) and quantity involved (where known), the route of exposure and the outcome of the incident which was reported as the method of disposal of the patient out of the A&E department (e.g. discharge, admission, died in A&E department). Each questionnaire also included a direct question about whether the incident occurred at work. Completed questionnaires were returned on a weekly basis, evaluated and stored on the Poisons Unit (PU) computer.

Out of a total of 22,195 completed questionnaires so far analysed, only 14 cases of acute or suspected acute paraquat poisoning have been identified. Of these, 9 occurred in males and 5 in females. The ages ranged from 1 to over 65 years, with 5 cases presenting in the under 16 age group. All the patients were discharged from A&E, except for one case who was admitted to intensive care and 3 who were admitted to medical wards. In the final analaysis, a total of approximately 26 000 questionnaires will be examined.

This project will, when complete, provide information about acute poisoning or suspected acute poisoning in a population of approximately 10 million in England and Wales. Since information has been gathered on all cases of acute poisoning or suspected acute poisoning seen in these A&E departments of hospitals which are in widely varying geographical locations, it should be less biased than the enquiries received by the PU on the incidence and effects of poisoning.[1]

In conclusion, it is interesting to note that these preliminary results show paraquat poisoning or suspected poisoning to be relatively infrequent for any individual A&E in England and Wales and therefore presenting them with a relatively minor although potentially serious problem.

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Aspects of Paraquat Poisoning in Greece

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The problem of paraquat poisoning in Greece has increased since 1976. In 1976 there were only 2 cases of poisoning, increasing to 12 in 1979. After 1980 there was a significant increase (25 cases) and 86 cases were reported in 1984. In 1985, the number of poisoning cases decreased to 60. We believe that this decrease is related to public awareness of the toxicity of paraquat after a campaign by the Poisons Information Centre through the press, television and radio. In the spring of 1985, a substance with a disgusting smell and a strong blue die was added to paraquat formulations, which made it much more difficult to accidentally ingest paraquat. Of the 231 reported cases in the last 3 years (1983–1985), 110 were mild intoxications due to either inhalation of the material or to eye or skin contact which produced local or no symptoms. Eighty-five of the remaining 121 cases were suicidal attempts. Sixty-five percent of all cases involved females and 35% males, whereas 80% of the suicidal cases involved females. The mortality rate for cases with severe poisoning was 38%. We have noted that the number of cases from certain geographical areas of the country, notably the island of Crete (25% of the total) account for the disproportionately large number of cases when compared to population size. Up to 1984 paraquat could only be detected in urine samples. From the spring of 1985 determination of paraquat in plasma samples by radioimmunoassay became available. Although the number of estimations is quite small the method is quite helpful in determining prognosis. The severity of paraquat poisoning could be decreased if the concentration of the commercial solution was decreased from 20 to 10%.

SHORT REPORTS

6 | 1 HUMAN TOXICOLOGY

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EDITORIAL

PAPERS

continued on inside back cover