DRAFT

EFFECT OF THE ADDITION OF AN EMETIC TO PARAQUAT FORMULATIONS ON ACUTE POISONING IN MAN

HART, T. B. and WHITEHEAD, A.

SUMMARY

In an effort to minimise the risk of accidental poisoning by ingestion of paraquat formulations, the manufacturer has added an emetic to the products containing paraquat. The addition was shown in animal models (dog and monkey) to increase the potentially lethal oral dose of paraquat by a factor of 3-5. This survey was designed specifically to examine the effects of this addition on paraquat poisoning in man.

640 cases of paraquat poisoning were reviewed, out of which 230 patients had swallowed the product containing emetic. In those patients swallowing the 'emeticised' product, 97% vomited spontaneously, compared with 65% of a retrospective control group who had swallowed 'non-emeticised' product. The speed of onset of vomiting as a result of the emeticised product was usually within 30 minutes of ingestion.

Comparison of the group of patients poisoning with 'emeticised' product with another retrospective control group involving 'non-emeticised' product shows that the mortality of paraquat poisoning has fallen from 84% to 64% for liquid formulations and from 21.5% to 12% for solid formulations following introduction of the emetic. It is unlikely that improved treatment or smaller doses of paraquat swallowed have caused this reduction, but it is difficult to conclude with any degree of certainty that the emetic addition is solely responsible.

As the emetic has been shown to reduce the toxicity of paraquat in animal models and it is an effective, reliable emetic in man, even in the presence of paraquat, this reduction in mortality of paraquat poisoning may well be due, in part, to the addition of emetic. This addition has not been shown to be associated with any serious adverse effects associated with the use or abuse of paraquat and as it may protect cases of accidental poisoning with paraquat, it is probably better to add emetic to paraquat formulations than to exclude it.

INTRODUCTION

Paraquat, (1,1 dimethyl-4-4'bipyridillium) was discovered as a herbicide in the 1950's and first sold as a product in 1962. The most common formulation of paraquat available worldwide is Gramoxone, an aqueas solution containing 200g per litre of paraquat ion. This formulation is now sold in over 130 countries throughout the world. In the United Kingdom, paraquat is also sold as a lower strength solid formulation, Weedol or Pathclear, containing 2.5% w/w paraquat and 2.5% w/w diquat, for use by the amateur gardener.

Although paraquat has been shown to be safe in normal use[1,2,3,4,5], regrettably its abuse, associated invariably with ingestion of the product, has been responsible for a number of fatalities. In the United Kingdom, the vast majority of abuse arises from suicide[6] and the incidence of fatal accidental poisoning remains very low. Nevertheless in order to further minimise the risk of accidental fatality from swallowing, the manufacturer has added several chemicals to the formulations. Two of these, a pyridine-based chemical designed to produce an odour and a blue dye have been added to warn people, who may be about to drink concentrated liquid paraquat formulation. The third is an emetic, which has been added to the formulation as a built in first-aid measure.

Prior to the addition of this emetic, a number of selection criteria had to be met. These included:-

1. The emetic should be sufficiently rapid in action.

2. The emetic must be effective, in the presence of paraquat, in removing toxicant from the stomach and increasing the potential lethal oral dose.

3. The emetic must not interfere with the safety of paraquat to man and his environment, associated with normal use.

4. The emetic must be physically compatible and miscible with paraquat in the formulations and must not interfere with the herbicidal action of paraquat.

codenamed PP796, was chosen as the emetic, because during its development as a drug for obstructive airways disease, it was found to be a very potent emetic in man with a rapid onset of action. A single oral dose of 5mg of emetic in an adult was considered sufficent to cause vomiting. It was also considered preferable as it was centrally acting, as opposed to an irritant or peripherally acting emetic. Irritant chemicals can enhance paraquat absorption across membranes. Finally, it fulfilled all the above selection criteria, particularly the second criterion. In animal models (dog and monkey) the potential lethal dose was increased by a factor of 3-5 fold[7] in the presence of emetic.

As a result, this emetic was introduced into paraquat formulations at a concentration of 0.05% w/v, or w/w equivalent to 5mg emetic in 10ml of Gramoxone or 1.5 sachets of Weedol/Pathclear. Thus the emetic was added at a concentration that would cause voimiting should the minimum protential lethal dose of paraquat formulation be swallowed.

The aim of this paper is to review the information from human cases of paraquat poisoning to determine how applicable the animal data is to man. In particular to assess:-

1. How effective the emetic is, in the presence of paraquat, in causing vomiting in man?

2. What effect, if any, has the emetic had on the mortality of paraquat poisoning?

3. What adverse effects, if any, has the emetic addition had?

METHODS

1. Patient Records

The study involved detailed questionnaire and follow-up of patients in the United Kingdom as described by Hart and Bramley[6] (1983). In particular, effort was made to determine details of the product involved and whether or not the emetic was present. The latter was achieved by one or more of several methods, including indentification of the product label (Figure 1), analysis of the original product for presence of emetic and analysis of the patient's urine for the presence of emetic metabolite.

Analysis of the patient's urine for emetic metabolite is a useful means of confirming emetic involvement, but cannot be used to determine its absence. A negative result may be due to emetic absence, but could also arise in patients who have swallowed low doses of paraquat and emetic, in which case emetic metabolite levels may be undetectable or in patients, whose urine was collected too late. (emetic metabolite is usually undetectable in urine taken after 48 hours of ingestion).

2. Control Group

As this study was conducted after introduction of the emetic into United Kingdom formulations and it is extremely difficult to prove absence of emetic involvement, a retrospective control group of paraquat poisoning cases, not involving the emetic, was used.

3. Analysis

The presence of emetic in the original product was analysed by [redacted]

Urine analysis for presence of the emetic metabolite was done using [redacted]

RESULTS

1. General Statistics

The survey has reviewed a total of 640 cases of proven paraquat poisoning out of which [redacted] were fatal and [redacted] non fatal. The majority of these cases ([redacted] of the total) were associated with suicidal ingestion and [redacted] of all fatalities were suicides. Paraquat poisoning is more common in males, [redacted], than females [redacted] and poisoning in children is rare ([redacted] cases, all non-fatal).

2. Emetic Cases

The emetic was confirmed as being involved in 230 cases (36% of the total) and in 78 of these, the emetic metabolite was detected in the patient's urine.

3. Effectiveness of Emetic in Causing Vomiting

Only those patients swallowing more than 10ml of Gramoxone or 1.5 sachets of Weedol/Pathclear were considered. Of the 69 patients, who met the above criterion and on whom sufficient information was available, 67 (97%) vomited spontaneously. Spontaneous vomiting is defined, in this context, as vomiting solely due to ingestion of the product.

Figure 2 illustrates the speed of onset of spontaneous vomiting. The majority of patients (64%) vomit within 30 minutes of ingestion and 94% vomit within 1 hour of ingestion.

4. Effect of Addition of Emetic to Paraquat Formulations on Mortality of Poisoning

Table 1 summarised the mortality statistics for patients who have ingested 'non-emeticised' paraquat formulations. These are considered under two categories - low strength solid formulations (Weedol/Pathclear) and concentrated liquid formulations (Gramoxone/Dextrone). Similarly Table 2 summarises the mortality statistics for paraquat formulations, containing emetic, considered in the same categories as in Table 1.

The mortality rate for poisoning with solid and liquid paraquat formulations not containing emetic is 21.5% and 84% respectively, but for similar formulations containing emetic, it is considerably lower with a 12% and 64% mortality rate respectively.

FIG 2.

EMETIC - SPEED OF ACTION

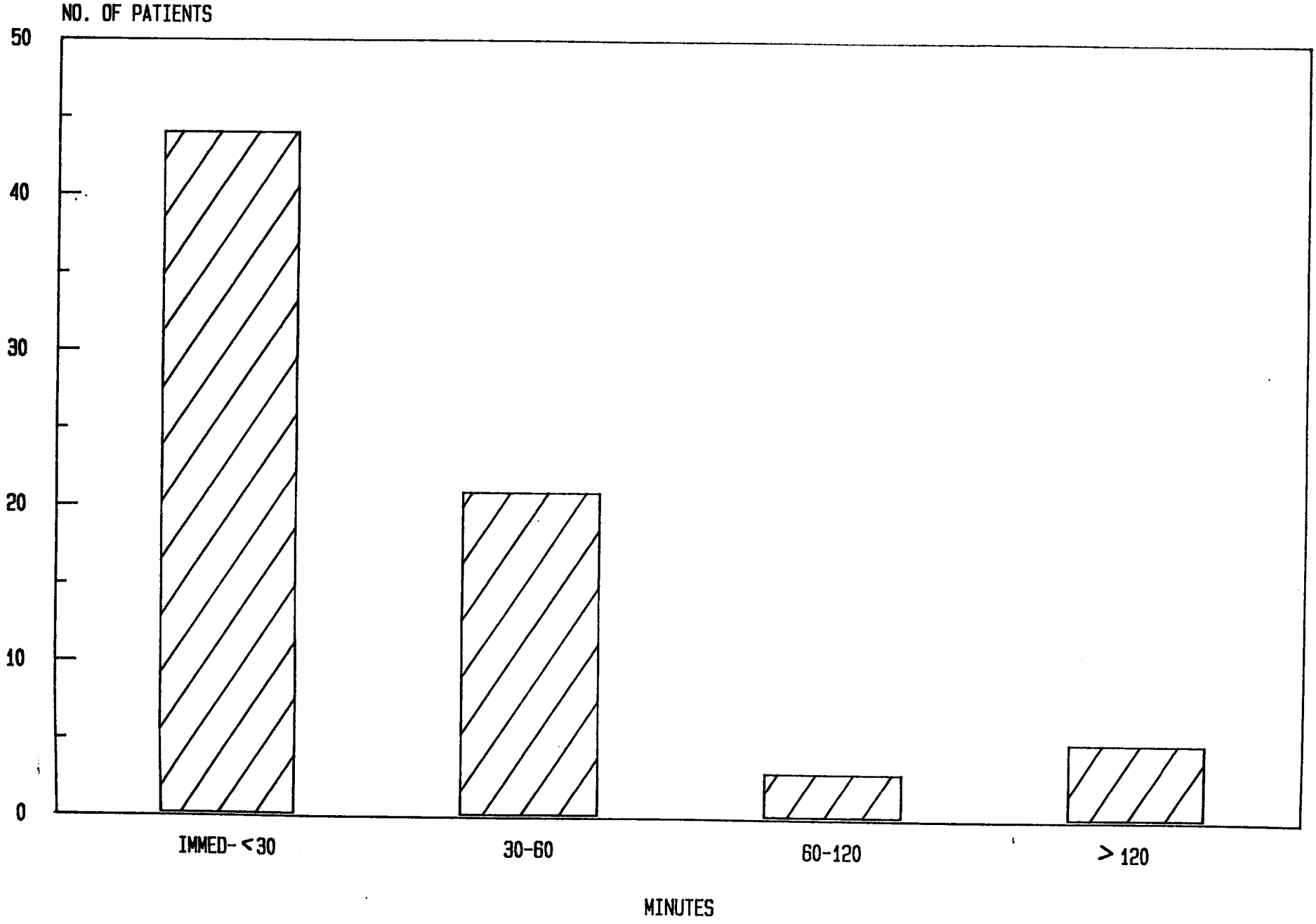

TABLE 1

MORTALITY OF NON-EMETIC PARAQUAT POISONING

	Fatal	Non-Fatal	% Mortality	
Solid Formulations				
Weedol	38	131	22.5)	21.5
Pathclear	1	11	8.3)	
Liquid Formulations				
Gramoxone	119	18	87)	84
Dextrone	4	5	44)	

TABLE 2

MORTALITY OF EMETIC PARAQUAT FORMULATIONS

	Fatal	Non-Fatal	% Mortality	
Solid Formulations				
Weedol	14	116	11)	12
Pathclear	5	25	17)	
Liquid Formulations				
Gramoxone	40	20	67)	64
Dextrone	1	3	25)	

TABLE 3

POTENTIAL LETHAL ORAL DOSE OF PARAQUAT (HUMAN)

Dose of Paraquat Ion Reported as being Swallowed	No Fatal	No Non-Fatal	% Mortality
<2 g	10	93	9
3 to <5 g	29	23	56
5 to <10g	18	2	90
10g or more	43	0	100

TABLE 4

PARAQUAT DOSE PROFILE
NON-EMETIC/EMETIC GROUPS

Dose of Paraquat Swallowed (GM. PQ. ION)	Number of Patients (as % of total) swallowing			
	Solid Formulations		Liquid Formulations	
	Non-Emetic	Emetic	Non-Emetic	Emetic
<2	81%	84%	6	15
2 - <5	16%	15%	9	26
5 - <10	3%	1%	25	26
10+	0%	0%	60	33
TOTAL NO OF CASES	145	352	110	176

DISCUSSION

The potential lethal oral dose of paraquat in man, has often been cited as 10-15ml of Gramoxone, equivalent to 3g of paraquat ion. We can confirm that this dose is more or less correct by studying doses said to have been ingested by patients. All cases refer to ingestion of non-emeticised paraquat and these are summarised in Table 3. As can be seen, increasing doses of paraquat are associated with higher mortalities. Furthermore, doses of 2 to 5g of ingested paraquat, equivalent to between 10 and 25mls of Gramoxone are associated with about 50% mortality. From the above, we can conclude that the potentially lethal oral dose of paraquat to man is between 2 and 5g of ion equivalent to 10 to 25ml of Gramoxone.

The addition of emetic to paraquat formulations has been shown, using animal models, to increase the potential lethal oral dose by a 3-5 fold factor. If the same is true for man, then the potentially lethal oral dose of 15ml should be increased to approximately 50ml of Gramoxone. Such a dose is rather more than a mouthful (approximately 30-40mls) and should cover those individuals who swallow Gramoxone accidentally. Suicides with paraquat may swallow much more than 50ml Gramoxone and therefore the emetic in these cases is unlikely to be of significant benefit.

The addition of the emetic to paraquat formulations produces a rapid onset of vomiting in the majority of patients (97%) who swallow the product. Paraquat itself is irritating to the gastro-intestinal tract and may produce vomiting. Howard (1979) reviewed 68 cases of paraquat poisoning involving non-emeticised product. About 50-60% of this group vomited spontaneously, but analysis of the original data shows that in 45 cases swallowing more than 10ml of Gramoxone or 1.5 sachets of Weedol or Pathclear, that is similar in doses as the 'emeticised' formulation cases involved, 65% of the patients vomited spontaneously. Hence it can be concluded that the addition of emetic to paraquat formulations has markedly improved the reliability of induction of vomiting. In most cases the addition of emetic has led to an early onset of vomiting.

Comparison of tables 1 and 2 shows that since the addition of the emetic, the mortality of both the solid and liquid formulations of paraquat has fallen from 21.5% to 12% for solid formulations and from 84% to to 64% for liquid formulations. The difference in mortality rates between solid and liquid formulations is undoubtedly due to the different concentrations and therefore acute toxicities of the two formulation types. However it is difficult to positively conclude that the reduction in mortality from 84% (liquid) and 21.5% (solid) for 'non-emeticised' formulations to 64% (liquid) and 12% (solid) for 'emeticised' formulations, is solely due to the addition of emetic.

A number of factors will influence the mortality statistics and we have tried to take into account as many of these as possible in forming our conclusions. One factor, which is important, is the treatment given to patients in the 'non-emeticised' and 'emeticised' groups. The treatment for a paraquat poisoning was developed and made available to doctors as early as 1974. Since then it has changed very little. The majority (73%) of the patients in the 'non-emeticised' group occurred after this date, so that treatment is unlikely to be a influencing factor on the mortality rates.

Another possible factor is that the patients in the two groups may have on average swallowed different doses of paraquat. Table 4 shows the type of doses of paraquat swallowed by patients according to the type of formulation involved and whether or not it contained emetic. In the case of the solid formulations, there is very little difference between the two groups, but rather more cases (as a percent of the total) swallowed smaller doses of emeticised liquid formulation compared with the non-emeticised product. It is unlikely that these differences have influenced the reduction in mortality from paraquat poisoning, because the reduction in poisoning mortality with solid formulations containing emetic is far greater (44%) than that involving the liquid formulations (24% reduction).

In spite of the above, it is not possible to account for every influencing factor, and therefore caution must be used when drawing conclusions from the data. However, in view of the fact that the emetic addition has been shown to lower the toxicity of paraquat in animal models and has been shown to cause reliable and rapid onset of voimiting in man, it is likely that this reduction in paraquat poisoning mortality may be due in part to the presence of emetic.

The survey showed very little evidence of serious untoward effects associated with use or abuse of the emticised paraquat formulations. The occasional instance of persistant vomiting and fluid and electrolyte inbalance was attributed to the emetic, but these were very few in number. Therefore on the basis that the emetic addition may well help protect accidentally poisoned patients with paraquat and is unlikely to be harmful, we believe it is better to have the emetic in the formulations than to exclude it.

TBH/MN
11.9.84.
TBH2

REFERENCES

1. Swann, A.A.B. (1969)
   Exposure of Spray Operators to Paraquat.
   Brit. J. Ind. Med. 26 322-329.

2. Hearn, C.E.D., and Keir, W. (1971)
   Nail Damage in Spray Operators Exposed to Paraquat.
   Brit. J. Ind. Med. 28 399-403.

3. Howard, J.K. (1979).
   A Clinical Survey of Paraquat Formulation Worker.
   Brit. J. Ind. Med. 36 220-223.

4. Howard, J.K. (1980)
   Paraquat : A Review of Worker Exposure in Normal Usage.
   J. Soc. Occup. Med. 30 6-11.

5. Howard, J.K., Sabapathy, N.W., and Whitehead, P.A. (1981).
   A Study of the Health of Malaysian Plantation Workers with Particular Reference to Paraquat Spraymen.
   Brit. J. Ind. Med. 38 110-116.

6. Hart, T.B. and Bramley, A. (1983).
   Paraquat Poisoning in the United Kingdom.
   Human Toxicology 2 417.

7. Rose, M.S. (1976).
   The Effect of Administration of an Emetic (PP796) on Paraquat Toxicity in Dog and Monkey.
   ICI Central Toxicology Laboratories - internal report.

8. Howard, J.K. (1979).
   Recent Experience with Paraquat Poisoning in Great Britain.
   A review of 68 cases.
   Vet. and Human Tox. 21 suppl. 213-216.

9. 'The Treatment of Paraquat Poisoning - A Guide for Doctors'.
   ICI Booklet Publication.