# **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

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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 paraguat 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 paraguat 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 nonemetic 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)<sup>a</sup> 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*

<sup>a</sup> Mean ± SD

\* Not significant

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

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 ( $\chi^2$  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

Group

Non-emetic formulation

Emetic formulation

(n = 21)

(n = 40)

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 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)]

< 2

1/10 (10)

16/29 (55)

Amount of paraquat ion ingested (g)

2-5

1/4 (25)

>5

2/7 (29)

3/4 (75) 7/7 (100)

 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		5
Group	< ½ h	$> \frac{1}{2}h$	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

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

the extremely low recovery of paraquat, it was hypothesized that either absorption must have occurred rapidly from the small intestine (peak plasma concentration  $\leq 60$  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 30year-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<sub>3</sub>/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 paraguat 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  $\mu$ mol/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 <sup>e</sup> (g of paraqual/100 g)
Kaolin	0.5
Decalso b	1.4
Amberlite	1.7
Bentonite	5.0
Fuller's Earth	5.0

<sup>a</sup> Calculated on the basis of a 1 mg/l limit of detection <sup>b</sup> 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]

Adsorhent	Time after dosing (h)	Paraquat dose and mortality <sup>a</sup> (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

" LD<sub>50</sub> 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 6Maximum (MAC) and strong (SAC) adsorptioncapacities of various materials [adapted from S. Okonek,H. Setyadharma, A. Borchent & E. G. Krienke (1982)Klin. Wochenschr., 60, 207-210]

Adsorbent	MAC (g of paraqual 100 g)	SAC <sup>a</sup> (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	>8	<1.0
(Kohle-Compretten,		
Merck)		

" 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.

	Time after dosing (h)	Paraquat dose and mortality <sup>a</sup> (mg/kg)	
Adsorbent		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	0.5	0/6	2/6
(Kohle-Compretten,	1.0	0/6	4/6
Merck)	2.0	0/6	4/6
	3.0	2/6	5/6

" LD<sub>50</sub> 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 <sup>a</sup>	

" P < 0.01

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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

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

Adsorbent	MAC (g of paraqual/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"	> 10	
Kalimate <sup>b</sup>	> 10	

<sup>a</sup> Sodium polystyrene sulphate

<sup>b</sup> Calcium polystyrene sulphate

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.

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