Reviews in Medicine

Clinical toxicology

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Introduction

Self poisoning is the second most common cause of acute medical presentation to hospital in the UK. However, as a result of changes over the last decade both in the amount and type of agent ingested, the majority of patients now suffer little if any adverse consequence and so require no active medical intervention. Nonetheless, a substantial minority of poisoned patients do still require skilled medical management, often using the facilities of an intensive care unit, if they are to survive without any important sequelae. Supportive therapy, including the correction of metabolic abnormalities, is of paramount importance in the care of such severely poisoned patients and this approach alone has reduced the mortality significantly. Occasionally, the use of a specific antidote will be life-saving but in few patients is such treatment either appropriate or necessary.

Procedures to reduce the absorption of ingested poisons have been employed widely for decades in the management of intoxicated patients. However, evidence of substantial clinical benefit to the majority of patients undergoing such treatment is lacking. Moreover, there is no general agreement as to which therapeutic approach is best. In addition, the value of procedures to increase elimination such as forced diuresis, dialysis and haemoperfusion is also being questioned and there is much present support for the use of activated charcoal both to reduce absorption and to increase elimination.

This review will assess critically firstly, the value of gastric lavage, activated charcoal and syrup of ipecacuanha in reducing poison absorption and secondly, the use of procedures to increase elimination.

Reducing absorption

Unfortunately, few clinical studies have been performed to determine the most beneficial approach.

Much of the relevant literature relates to studies in volunteers given either a non-toxic marker or a non-toxic dose of a drug. As a result, the extrapolation of many of these data to the poisoned patient cannot be done with confidence.

Gastric lavage

Although 'the idea of washing out the stomach with a syringe and tube, in cases where large quantities of laudanum and other poisons had been swallowed,' was first reported by Physick¹ in 1812 the value of gastric lavage remains controversial. Lavage performed 60 minutes after a therapeutic dose (1 g) of aspirin had been administered to volunteers did not produce any significant reduction in the absorption of aspirin² as judged by salicylate recovery in the urine. Similarly, no significant reduction in the area under the curve relating plasma drug concentration to time after its administration (AUC) was noted after volunteers had been subjected to lavage 60 minutes after the administration of 5 g ampicillin.³ Tandberg *et al.*⁴ found that lavage 10 minutes after the administration of cyanocobalamin as a marker, resulted in a mean recovery of cyanocobalamin of $45 \pm 13\%$; this study, however, has little relevance to clinical practice due to the very early use of lavage.

Allan,⁵ after reviewing the use of gastric lavage in 68 cases of barbiturate poisoning and finding that an average of only 117 mg barbiturate was recovered, concluded that the technique was 'potentially dangerous in all cases and of no value in most'. It was Matthew *et al.*⁶ who established, in patients poisoned with barbiturates, that lavage less than 4 hours post-overdose was likely to be more efficacious than later lavage. However, only 37% of those lavaged early had more than 200 mg barbiturate recovered in the lavage fluid; in only 1% of patients lavaged after 4 hours was more than 200 mg recovered. In the case of salicylate poisoning, only 26% of all patients lavaged had more than 1,000 mg recovered in the lavage fluid.⁶

Despite seemingly adequate lavage, drugs may be found in the stomach at post mortem but this is

not surprising as even the largest bore orogastric tube may be inadequate to allow the removal of a bezoar of tablet/capsule debris from the stomach. Recent evidence indicates that even after lavage most (88%) patients may still have residual intragastric solid.⁷ In addition, lavage may cause gastric contents to be discharged into the small bowel, thereby increasing the amount of drug available for absorption.⁸ Moreover, continued absorption of drugs after lavage is known to occur.⁹

Comstock *et al.*⁹ evaluated the efficacy of lavage in 62 patients of whom 40% were lavaged within 2 hours of overdose. Unfortunately, very limited drug sampling was undertaken and even before lavage therapeutic drug concentrations were present in 52% of patients. The authors concluded that except in the case of tricyclic antidepressant poisoning and massive overdose, poor recovery of drug was likely if lavage was performed more than 2 hours after overdose. Yet, in another study,¹⁰ the mean amount of tricyclic antidepressant recovered in 13 patients who were moderately or severely poisoned was only 109 mg at a mean time of 6 hours post-overdose.

In a comparative study of volunteers, gastric lavage was shown to be significantly better than syrup of ipecacuanha in reducing drug absorption⁴ but of similar value to syrup of ipecacuanha in two other studies,^{2,3} probably because the latter two studies were performed at 60 minutes post-dosing, whereas the first study involved assessment at 10 minutes.

Auerbach *et al.*¹¹ performed lavage on 37 patients, 34 of whom were drowsy or obtunded (comatosed) when the procedure was performed. A further 51 patients, all of whom were fully conscious, were each given syrup of ipecacuanha. Both groups of patients received thiamine as a marker when lavage was performed or syrup of ipecacuanha was administered. Thiamine recovery was significantly greater following lavage than after syrup of ipecacuanha administration. Kulig *et al.*¹² assessed the value of gastric lavage in 72 obtunded patients who also received supportive care and activated charcoal. Gastric lavage led to a better outcome only if performed within one hour of ingestion of overdose.

A further study published recently¹³ has assessed the value of aspiration (but not lavage) of stomach contents in 50 patients inebriated with alcohol. Although a significant amount of ingested alcohol could occasionally be removed by this technique, there was no way of identifying on presentation which patient would benefit and the routine use of gastric emptying in the detoxification of inebriated patients, therefore, cannot be recommended.

Complications of use The potential complications of gastric lavage are well documented though in

practice are observed only infrequently. These include temporary cyanosis and laryngospasm during the procedure; conjunctival haemorrhages; mechanical injury to the gut (though perforation is exceedingly rare, occurring in approximately 1 in 5,000 cases); aspiration pneumonia, which is particularly likely to occur if petroleum distillates have been ingested and lavage is carried out without an endotracheal tube *in situ*; water intoxication in young children as a result of overzealous lavage; cardiac arrhythmias¹⁴ and enhanced drug absorption.⁹

Syrup of ipecacuanha

Syrup of ipecacuanha contains two alkaloids, emetine and cephaeline, which act upon the vomiting centre after absorption; in addition, emetine is an impressive gastric irritant and causes vomiting usually within 30 minutes in ingestion. Provided that the dose of syrup of ipecacuanha is appropriate for the age of the patient, and a second dose is administered within 20 minutes if necessary, 100% of children¹⁵ and more than 90% of adults¹⁶ will vomit.

Syrup of ipecacuanha has been shown to reduce significantly the peak drug concentration (C_{max}) and AUC of aminophylline,¹⁷ cimetidine,¹⁸ paracetamol¹⁷ and pindolol¹⁸ if administered 5 minutes after a therapeutic dose of drug in volunteers. The C_{max} and AUC of tetracycline were also reduced significantly¹⁷ when syrup of ipecacuanha was administered both at 5 minutes and 30 minutes post-dosing. The mean AUC of ampicillin³ and paracetamol¹⁹ was also reduced significantly when syrup of ipecacuanha was given 60 minutes after drug dosing. However, it should be noted that in another study¹⁷ the C_{max} and AUC of paracetamol were not reduced significantly when syrup of ipecacuanha was given at 30 minutes. In the same study,¹⁷ syrup of ipecacuanha did not reduce significantly the absorption of aminophylline when it was given at 30 minutes.

The recovery of urinary salicylate was significantly reduced by the administration of syrup of ipecacuanha 60 minutes post-dosing in one study²⁰ but not in another,² possibly due to differences in study design. Syrup of ipecacuanha reduced tilidine absorption when given at 3 minutes but not at 25 minutes.²¹ In three other volunteer studies, the mean recovery of marker was 83% at 5 minutes,²² 28–47% at 10 minutes,^{4,23} 59% at 30 minutes and 44% at 60 minutes²² post-marker administration. It is noteworthy that the recovery of marker in individual volunteers varied widely even when syrup of ipecacuanha was administered soon after marker administration. The value of syrup of ipecacuanha has also been assessed in several clinical studies. In the first two studies a marker was

administered simultaneously with syrup of ipecacuanha and mean recoveries of 28%²⁴ and 50%¹¹ were achieved.

In a further study, Amitai *et al.*²⁵ calculated the predicted 4 hour paracetamol concentration based on the history obtained from the child's parents and so estimated the ratio of measured/predicted drug concentration following syrup of ipecacuanha administration. Overall, those who received syrup of ipecacuanha within a mean time of 26 minutes had a 75% reduction in the predicted paracetamol concentration but all predicted and measured paracetamol concentrations were below the threshold for treatment with a protective agent such as N-acetylcysteine. The necessity for this treatment approach must, therefore, be questioned as the use of syrup of ipecacuanha does not appear to have altered the outcome. In addition, Kulig *et al.*¹² have shown in a clinical study that syrup of ipecacuanha (followed by the administration of activated charcoal) did not alter the outcome beneficially in 214 patients who were alert on presentation.

Why is syrup of ipecacuanha ineffective? Sætta and Quinton⁷ have demonstrated that after the administration of syrup of ipecacuanha 38.5% of patients had residual intragastric solid in their stomach at endoscopy. Moreover, these workers also showed in a further study⁸ that syrup of ipecacuanha propels gastric contents into the small bowel and might, therefore, enhance drug absorption.

Complications of use There is good evidence that the administration of syrup of ipecacuanha may produce persistent vomiting, diarrhoea, lethargy and drowsiness in up to 15% of those so treated.^{26,27} These features mimic those produced by many drugs in overdose and, thus, the use of syrup of ipecacuanha may make it more difficult to interpret the clinical significance of early signs and symptoms. Of greater concern is the fact that aspiration pneumonia has been reported even in those patients given syrup of ipecacuanha when they were fully conscious.^{12,28} Albertson *et al.*²⁸ compared syrup of ipecacuanha and activated charcoal (93 patients) with activated charcoal alone (107 patients) in adults with 'mild/moderate overdose' who were awake with a gag reflex and who had no previous history of vomiting and who had not been given syrup of ipecacuanha at home. Patients receiving syrup of ipecacuanha spent significantly longer in the Emergency Department and suffered significantly more complications than those receiving activated charcoal. Four out of five patients suffering complications from syrup of ipecacuanha were observed to aspirate and three developed pneumonitis. A further patient had, what was presumed to be, an ipecacuanha-induced threatened abortion.

Rarely, isolated cases of Mallory–Weiss syndrome^{29,30} herniation of the stomach into the pleural cavity³¹ and gastric rupture,³¹ have been reported and fatalities have occurred^{31,32} following the use of syrup of ipecacuanha.

Activated charcoal

Charcoal is prepared from vegetable matter, usually peat, coal, wood, coconut shell and petroleum. Charcoal is 'activated' by heating it at high temperature either in a stream of gas (such as steam or carbon dioxide) or with a chemical activating agent (such as phosphoric acid or zinc chloride) or by a combination of both processes. The process of activation creates a highly developed internal pore structure and thereby increases the surface area from 2–4 m²/g to an area in excess of 1,000 m²/g (for example, Carbomix); super-activated charcoals (for example, 'Super-char' (PX21)) have a surface area in excess of 2,500 m²/g.

Activated charcoal significantly reduced the $C_{\max}$ and AUC of disopyramide,³³ indomethacin,³³ paracetamol,¹⁷ phenylbutazone³⁴ and trimethoprim³³ when it was administered within 5 minutes of the administration of a therapeutic dose of each drug to volunteers. Activated charcoal not only reduced the $C_{\max}$ and AUC of aminophylline when administered at 5 minutes but also when it was given at 30 minutes post-dosing.¹⁷ In addition, activated charcoal also reduced significantly the absorption of doxepin³⁵ and tetracycline¹⁷ when it was administered at 30 minutes post-dosing. Neuvonen *et al.*¹⁷ showed that paracetamol absorption was reduced significantly by activated charcoal when it was administered at 5 minutes but not at 30 minutes though, in another volunteer study, McNamara *et al.*¹⁹ demonstrated a significant reduction in paracetamol AUC when activated charcoal was given at 60 minutes; sorbitol did not enhance the benefit of charcoal.³⁶ The administration of activated charcoal at 60 minutes post-dosing also reduced significantly the absorption of ampicillin,³ aspirin,^{20,37} carbamazepine,³⁴ digoxin,³⁸ mefenamic acid,³⁹ phenobarbitone,³⁴ phenytoin,³⁸ theophylline⁴⁰ and tolafenamic acid.³⁷ The absorption of isoniazid,⁴¹ mexiletine³⁷ and phenylbutazone,³⁴ was not decreased significantly by charcoal when it was given 60 minutes post-therapeutic dosing.

Other studies have evaluated the impact of activated charcoal on the recovery of drug metabolites in urine. Charcoal was shown to reduce recovery of metabolites if administered at 5 minutes in the case of cimetidine¹⁸ and pindolol,¹⁸ at 25 minutes in the case of tilidine²¹ and 60 minutes in the case of digoxin³⁸ and aspirin,²⁰ though this latter benefit was not demonstrated in two other studies.^{2,38}

In summary, there is evidence from volunteer

studies that activated charcoal administered at 60 minutes post-dosing will prevent significant absorption of the following drugs: ampicillin,³ aspirin,^{20,37} carbamazepine,³⁴ digoxin,³⁸ mefenamic acid,³⁹ paracetamol,¹⁹ phenobarbitone,³⁴ phenytoin,³⁸ theophylline⁴⁰ and tolfenamic acid.³⁷ The clinical significance of these studies, however, is not clear as comparatively large doses (usually 50 g) of activated charcoal were administered to volunteers given only therapeutic drug doses. In addition, comparative studies in volunteers indicate that activated charcoal is superior both to syrup of ipecacuanha^{2,17,18,20,21} and gastric lavage.³ Furthermore, there is now clinical evidence in patients poisoned with paracetamol that activated charcoal is superior to gastric lavage and syrup of ipecacuanha in reducing drug absorption.⁴²

Complications of use It has long been recognized that the administration of several hundred grams of activated charcoal may produce severe constipation and gastrointestinal obstruction has been reported.⁴³ However, if only 50–100 g activated charcoal are given to reduce absorption, constipation is unlikely to be a significant clinical problem. Pulmonary aspiration of charcoal, particularly if it contains povidone (Medicoal), may lead to serious and even fatal sequelae.⁴⁴ Bronchiolitis obliterans has also been reported in a patient given both activated charcoal and sorbitol together.⁴⁵

Charcoal vs lavage vs syrup of ipecacuanha

The majority of patients presenting to hospital after an overdose are not seriously poisoned in a physical sense because they have not taken a substantial quantity of a toxic agent. The challenge for those managing such patients is to identify at an early stage those who are at most risk of developing serious complications in order that treatment aimed at reducing absorption can be employed. In our present state of knowledge it would seem reasonable to propose that activated charcoal 50–100 g should be administered to patients who have taken a substantial overdose of a toxic substance less than one hour previously. This may be done conveniently by using an orogastric tube, which would allow lavage to be undertaken with possible additional benefit.

Syrup of ipecacuanha should now be abandoned as there is little evidence of efficacy even in volunteer studies. Furthermore, the complications that follow the use of syrup of ipecacuanha even in conscious patients, particularly aspiration pneumonia, combined with the diagnostic difficulties which ensue as its effects mimic those of many overdoses, are further compelling reasons to reconsider its role.

Increasing poison elimination

There are four techniques currently available to increase poison elimination:

1. Forced diuresis alone or with pH manipulation.
2. Repeat dose activated charcoal therapy.
3. Dialysis.
4. Haemoperfusion.

To be valuable clinically, the rate of poison removal by any of these elimination techniques must be significantly greater than spontaneous rates of elimination by hepatic metabolism or renal excretion.

Rationale

Forced diuresis The filtrate produced by the glomeruli has a composition similar to that of plasma water but excludes molecules with a molecular weight of more than 66,000 daltons such as drug-protein complexes. Thus, only that fraction of a drug which is non-protein-bound is filtered. Some drugs are secreted actively into the proximal renal tubules against the concentration gradient. These include acidic drugs, such as the penicillins, sulphonamides, phenobarbitone, salicylates, phenylbutazone and probenecid, and organic bases, such as quinine, quinidine, amphetamine and procainamide. Drugs may also be eliminated by passive diffusion across the epithelium of the tubule into the lumen. As water is progressively reabsorbed from the tubular fluid as it passes distally, a favourable concentration gradient is created for the reabsorption of these dissolved substances back into the blood stream.

Tubular reabsorption is influenced by urinary flow rate. Diuresis therefore increases the renal clearance of drugs that are reabsorbed passively since the concentration gradient is reduced. Potentially, therefore, by increasing urine flow, drugs excreted largely unchanged by the kidney may be eliminated more rapidly.

Forced diuresis with pH manipulation Cell membranes are more permeable to substances that are lipid soluble and in the non-ionized, rather than the ionized, form. Thus, the rate of diffusion from the renal tubular lumen back into the circulation is decreased when a drug is maximally ionized. Because ionization of weak acids is increased in an alkaline environment, and that of basic drugs in an acid solution, manipulation of the urine pH can enhance renal excretion. For acidic drugs, there is a greater degree of ionization at pH 8 than 7.4 and, for basic drugs, a greater degree of ionization at pH 6 than at 7.4. Thus, the renal elimination of weak acids is increased in alkaline urine if the pK_a of the drug concerned lies in the range 3.0 to 6.5; for weak bases, elimination is increased in acid urine if the

pK_a of the drug lies in the range 7.5–10.5. Since pK_a is a logarithmic function then, theoretically, a small change in urine pH can have a disproportionate effect on clearance. Thus, the elimination of salicylate (pK_a 3.5) is increased in alkaline urine and urinary acidification will increase the elimination of amphetamines (pK_a 9.8). Urine pH may also influence the fraction of the total dose of drug which is excreted unchanged. Thus, about 57% of a dose of amphetamine is excreted unchanged in acid urine (pH 4.8–5.1) as compared to about 5% in subjects with alkaline urine (pH 7.6–8.3) (see below).

Repeat dose charcoal therapy The oral administration of substantial (and repeated) doses of activated charcoal is thought to produce its beneficial effect by:

1. Adsorbing any unabsorbed poison still present in the gut. This is particularly relevant in the case of slow-release preparations (for example, theophylline) or drugs which are slowly absorbed because of decreased gastric motility (for example, tricyclic antidepressants).
2. Adsorbing drugs which are secreted in bile, thereby preventing intestinal reabsorption.
3. Binding any drug which diffuses from the circulation into the gut lumen, thus interrupting the entero-enteric circulation. After absorption, a drug will re-enter the gut by passive diffusion provided that the concentration there is lower than that in blood. The rate of passive diffusion depends on the concentration gradient and the intestinal surface area, permeability and blood flow. Exceptionally, drugs such as digoxin may, in addition, be actively secreted by the intestinal mucosa, though this process is unlikely to contribute more than passive diffusion does to the effect of activated charcoal on drug clearance. Under these 'sink' conditions, a concentration gradient is maintained and drug passes continuously into the gut lumen where it is adsorbed.
4. A purgative action. This may be due either to the co-administration of sorbitol or the use of certain charcoal formulations (e.g. Medicoal) which produce diarrhoea rather than severe constipation after the administration of 100–200 g or more.

Peritoneal dialysis Although widely available, peritoneal dialysis is at least 2–3 times less effective than haemodialysis for the removal of poisons. In addition, since the delivery of toxins to the peritoneum is dependent on blood flow rate, the efficiency of this technique is reduced in the presence of hypotension. If metabolism contributes significantly to the total body clearance of an agent, dialysate clearance will be low and removal by this

means is therefore of little importance. Thus, even in the presence of renal failure, peritoneal dialysis has very limited application.

Haemodialysis Haemodialysis was first employed in 1913 for the removal of salicylic acid in experimental poisoning⁴⁶ but was not applied clinically until 1950 when it was used for the treatment of salicylate poisoning.⁴⁷ It was undertaken widely during the following two decades and, as a result, there are many reports of its apparent value in the treatment of acute poisoning.⁴⁸ Many of these accounts, however, are little more than anecdotal, or even self-adulatory, on the part of the authors. They commonly suffer from a dearth of analytical observations to support the published conclusions. Prescott⁴⁹ has examined data purporting to demonstrate the efficacy of haemodialysis and has shown that this method of treatment has often been carried out in patients who have had less than therapeutic plasma concentrations of a drug, or that amounts equivalent to little more than one tablet have been removed.

Haemoperfusion The major rate-limiting factors in removal of toxins by haemoperfusion (the passage of blood through an adsorbent material such as charcoal or resin) are the affinity of the adsorbent for the toxin, the rate of blood flow through the circuit, the volume of distribution of the toxin and the rate of equilibration of toxin from tissues to blood. Haemoperfusion is more efficient than haemodialysis in removing barbiturates and non-barbiturate hypnotics, though there are some differences between the performance of haemoperfusion systems using activated charcoal and XAD-4 resin. While activated charcoal adsorbs both polar and non-polar drugs, XAD-4 resin removes most non-polar drugs more efficiently than charcoal.

Haemoperfusion over 4–6 hours significantly reduces the body burden of compounds with a low volume of distribution (<1 litre/kg). For compounds with intermediate values (2–6 litres/kg), longer periods of haemoperfusion are necessary. Haemoperfusion cannot reduce significantly the body burden of those poisons which have very large volumes of distribution. Furthermore, although toxin clearance during haemoperfusion is a general guide to the efficacy of the technique, it may be misleading if only a small proportion of the body load of poison is removed.

Salicylate poisoning Alkaline diuresis has been employed in the management of salicylate poisoning for the last two decades.^{50–53} With increasing blood concentrations, the elimination of salicylate by the kidney assumes increasing importance. The renal clearance of salicylate is dependent on urine

pH. Morgan and Polak⁵⁴ have shown that there is a four-fold increase in renal clearance of salicylate for each rise of one unit in urine pH. Thus, renal salicylate clearance increased from 16 to 64 ml/min as urine pH increased from 6.5 to 7.5. Although the renal clearance of salicylate also increases with increasing urine flow, this effect is of less importance as urine pH rises. With supportive therapy alone, the plasma elimination half-life of salicylate at high plasma salicylate concentrations is approximately 30 hours,⁵⁵ whereas, with alkaline diuresis, it may be reduced to as little as 6.5 hours, even in severely poisoned patients.⁵⁶

The value of repeat dose activated charcoal has been assessed recently⁵⁷ in a volunteer study and it was found that salicylate clearance was not enhanced by its use. In contrast, Hillman and Prescott⁵⁸ have reported the value of activated charcoal in enhancing salicylate elimination in poisoned patients and the beneficial outcome in a further series of poisoned patients has also been published.⁵⁹ It should be noted that the patients reported by Hillman and Prescott⁵⁸ all had plasma salicylate concentrations below 500 mg/l at the time that charcoal therapy was commenced, whereas those in the Birmingham series⁵⁹ were more severely poisoned. This may explain the longer elimination half-life in the latter group (9.7 ± 3.0 hours)⁵⁹ compared with the group treated by Hillman and Prescott (3.2 hours).⁵⁸

In addition, Hillman and Prescott⁵⁸ administered a charcoal preparation that contained bicarbonate so that the urine pH of their patients rose, which would further enhance salicylate elimination. Although the administration of repeat dose charcoal is less metabolically invasive than alkaline diuresis, its use may not be possible in severely poisoned patients who are likely to be vomiting. Even if charcoal is tolerated in such patients, a well-conducted alkaline diuresis increases salicylate clearance more rapidly than repeat-dose charcoal, but it is appropriate to employ the latter as an adjunct both to reduce drug absorption and increase elimination.

Two patients so treated have been reported recently.⁶⁰ The respective salicylate elimination half-lives were 7.7 and 12.7 hours. In both patients, the plasma concentrations exhibited non-linear disposition, consistent with Michaelis-Menten kinetics, until between 36 and 41 hours post-ingestion when they changed to first-order kinetics.

Peritoneal dialysis has been shown to lower plasma salicylate concentrations, and to be less efficient than alkaline diuresis, it can be employed in the presence of renal impairment. Haemodialysis is four times more effective than peritoneal dialysis.⁴⁸

Phenylbutazone poisoning Data from a volunteer study³⁴ indicate that repeat dose activated charcoal reduces the plasma half-life of phenylbutazone. No data on poisoned patients have been published. In an *in vivo* study, Okonek⁶¹ found XAD-4 resin haemoperfusion to be unimpressive in removing phenylbutazone. However, it has been employed clinically^{62,63} and success for its use claimed. Clinical experience is too limited to know whether haemoperfusion is more effective than repeat dose activated charcoal, though this is doubtful.

Theophylline poisoning Both volunteer studies⁶⁴⁻⁶⁷ and clinical experience^{59,67-69} in poisoned patients suggest that repeat dose charcoal increases clearance and decreases the plasma half-life of theophylline. Theophylline elimination is concentration dependent and this, together with the differing doses of charcoal administered in these studies, is thought to explain the variability of half-lives found. In practice, it is often difficult to employ repeat-dose charcoal therapy because of intractable theophylline-induced vomiting, though the use of intravenous ondansetron is often helpful.

Clearance during peritoneal dialysis is of the same order as the endogenous theophylline clearance rate: in children aged 18 months and 34 months old, it was 1.3 ml/minute and 5.1 ml/minute respectively.^{70,71} In addition, Brown *et al.*⁷² found that theophylline clearance in adults during peritoneal dialysis was less than 12 ml/minute; only 4 mg was removed over a 48 hour period. Lee *et al.*⁷³ reported similar values (9.5 ml/minute). Thus, peritoneal dialysis is much less effective than haemodialysis which can achieve clearances of 112 ml/minute⁷⁴ in adults, if blood flow is maintained. When it is not, clearances between 33 and 88 ml/minute are obtained.^{75,76} Haemodialysis can therefore, be expected to double the total body clearance of theophylline but is less effective than haemoperfusion. Heath and Knudsen⁷⁷ have reviewed the value of haemoperfusion in theophylline poisoning. They concluded that 'of the invasive techniques available, charcoal haemoperfusion is the most effective, increasing clearance four-fold'. Haemoperfusion should be considered if the patient is severely poisoned and has a plasma concentration greater than 100 mg/l following an acute overdose or greater than 60 mg/l during chronic therapy. However, the use of supportive measures (including the correction of electrolyte and metabolic abnormalities) and the administration of repeat dose activated charcoal, with intravenous ondansetron if necessary, usually obviates the need for haemoperfusion.

Amphetamine poisoning Beckett *et al.*⁷⁸ demonstrated in volunteers that 57-66% of an administered dose of amphetamine was recovered

unchanged in a period of 6 hours in urines with pH values ranging from 4.8 to 5.1; less than 5% of the drug was removed when the urine was alkalized to a pH of 7.6–8.3. Davis *et al.*⁷⁹ have reported a shorter amphetamine plasma half-life (8–10.5 hours) with acid (pH 5.5–6.0) urine than with alkaline (pH 7.5–8.0) urine (16–31 hours). Anggard *et al.*⁸⁰ acidified the urine of three patients and alkalized the urine of four patients with amphetamine-induced psychosis. The plasma half-life of amphetamine in those with an acid urine was 7–14 hours and symptoms cleared rapidly. By contrast, the plasma half-life in the four cases with alkaline urine was 19–34 hours and psychosis was prolonged. Gary and Saidi⁸¹ also reported data which suggest that acid diuresis increases amphetamine elimination in patients poisoned with amphetamine. However, as rhabdomyolysis may complicate amphetamine intoxication, acid diuresis could increase the risk of associated renal failure. Furthermore, as acid diuresis is a difficult technique to undertake and, as it may increase morbidity, it should be considered only in those few patients who do not respond to sedation, either with diazepam, chlorpromazine or droperidol.

Fenfluramine poisoning Urinary acidification increases the renal elimination of fenfluramine⁸² but has never been employed widely and there are no published data on which to determine efficacy. Unpublished findings suggest that the amount of unchanged drug recovered in the urine is small. Furthermore, sedation with chlorpromazine, is invariably sufficient once the risk of early cardiac arrest has passed.

Digoxin and digitoxin poisoning There is evidence from a volunteer study⁸³ and from studies in poisoned patients^{84,85} that repeat doses of activated charcoal increase digoxin elimination. Similarly, the elimination of digitoxin is also increased by these means.^{86,87} In practice, vomiting may preclude this therapeutic approach. In addition, in severe cases, the use of digoxin-specific antibody Fab fragments would be more appropriate.

Disopyramide poisoning There is limited evidence that Amberlite XAD-4 resin (but not charcoal) haemoperfusion together with inotropic support may increase elimination sufficiently to prevent a fatal outcome in cases of severe poisoning,⁸⁸ though inotropic support alone has led to a full recovery, even in a very severely poisoned patients.

Nadolol poisoning In a volunteer study, the elimination half-life of nadolol was reduced from 17.3 ± 1.7 to 11.8 ± 1.6 hours by small doses of activated charcoal given over 9 hours.⁸⁹ The relevance of this observation to the treatment of

poisoned patients is doubtful, particularly as intravenous glucagon is so effective as an antidote.

Cyclosporin poisoning The administration of activated charcoal at a rate of 15 g/hour reduced the half-life of cyclosporin from 9 to 2.5 hours in a patient given 5 g by mistake following a transcription error.⁹⁰

Lithium Sodium chloride diuresis has been proposed as a useful means of increasing lithium excretion in intoxicated patients.⁹¹ Hansen and Amdisen,⁹² however, were unable to demonstrate any specific effect of sodium on lithium excretion since the fractional excretion of lithium did not change consistently during the sodium infusion, though many of these patients had impaired renal function due to lithium toxicity. Similarly, Jacobsen *et al.*⁹³ found that forced diuresis with sodium chloride did not increase renal elimination significantly. In contrast, Dyson *et al.*⁹⁴ have reported that renal lithium clearance is enhanced by increased sodium excretion. Although the precise role of forced diuresis in lithium intoxication has not been established, it is probable that forced diuresis with 0.9% sodium chloride will benefit patients prescribed lithium who are only mildly intoxicated and who also have normal renal function and a serum lithium concentration less than 3 mmol/l; after an acute overdose of lithium, saline diuresis should be considered in patients with serum concentrations up to 5 mmol/l. More severely poisoned patients in both categories usually require haemodialysis. Large infusions of sodium should be avoided in patients suffering from lithium intoxication because of the risk of producing hypernatraemia due to water-losing nephritis. Recently, MacDonald *et al.*⁹⁵ have advocated the use of low-dose dopamine in lithium intoxication on the basis that dopamine increases sodium excretion by a specific action on the proximal tubule. Further studies are required to confirm this single case observation.

Lithium can also be removed by peritoneal dialysis,^{92,96} though this technique is less efficient than haemodialysis. Clearances of 13–15 ml/minute have been achieved with peritoneal dialysis⁹⁷ compared with haemodialysis clearance values of 60–132 ml/minute.^{92,93,98–100} However, after haemodialysis there is often a rebound increase in serum lithium concentration due to the slow diffusion of lithium across cell membranes. Haemodialysis is the treatment of choice in severe lithium intoxication though there has been debate recently on when it should be employed and for what period.^{101,102} Following an acute overdose of lithium, haemodialysis may prevent lithium diffusion into the brain and the onset of severe toxicity. In contrast, those patients who develop intoxication during chronic therapy may require long periods of dialysis to produce clinical improvement.

Phenobarbitone poisoning Prescott⁴⁹ showed that the clearance of phenobarbitone is directly related to urine flow. In addition, Waddell and Butler¹⁰³ demonstrated in dogs that alkalization of the urine further increases the renal clearance of phenobarbitone. Similarly, Bloomer¹⁰⁴ showed that the renal clearance of phenobarbitone rises sharply as the urine pH exceeds 7.5. Prescott⁴⁹ has criticized these data and, in studies of his own in poisoned patients, has demonstrated that changes in urine pH had little effect on tubular reabsorption as shown by the ratio of the urine to plasma concentrations. Moreover, the maximum renal clearance of phenobarbitone achieved by alkaline diuresis¹⁰⁵ is of the order of 17 ml/minute, which compares poorly with that found with repeat dose charcoal therapy.

Neuvonen and Elonen³⁴ gave volunteers activated charcoal at 10, 14, 24, 36 and 48 hours after the oral administration of a therapeutic dose of phenobarbitone and found that the elimination half-life was reduced from a mean of 110 to 19.8 hours. Berg *et al.*¹⁰⁶ subsequently established that the non-renal elimination of *intravenous* phenobarbitone was also significantly increased by repeat-dose charcoal. Goldberg and Berlinger¹⁰⁷ administered repeated oral charcoal to two patients acutely poisoned with phenobarbitone and noted a reduction, not only in the elimination half-life to approximately 24 hours, but also in the duration of coma and the need for supportive care.

Pond *et al.*¹⁰⁸ attempted to confirm these findings in a randomized study of 10 comatose patients who required endotracheal intubation and mechanical ventilation. The control and treatment groups both received 50 g activated charcoal on presentation and, in addition, patients in the treatment group were given 17 g activated charcoal together with sorbitol 4 hourly until they had recovered sufficiently to be extubated. Although the mean elimination half-life of phenobarbitone was shortened to 36 ± 13 hours the length of time the patients took to recover sufficiently to need extubation (48 ± 8 hours) did not differ significantly from the control group and nor did the time spent in hospital. This trial has been criticized as being too small and having unevenly matched groups.^{109,110} In addition, the dose of activated charcoal was probably inadequate (4.25 g/hour) and the co-administration of a cathartic may have reduced the efficacy of activated charcoal.

In another study,¹¹¹ charcoal administered in larger doses (15.6–18.75 g/hour) and without cathartic not only greatly enhanced the elimination of phenobarbitone (mean half-life 11.7 ± 3.5 hours), but also decreased the time to recover consciousness (16 ± 9 hours). It should be noted that only one third of the patients in this series¹¹¹ were receiving long-term anticonvulsant therapy in con-

trast to 100% of patients in the Pond *et al.* study¹⁰⁸ and enzyme induction is not, therefore, the explanation for the more impressive reduction in half-life. In a fourth clinical study, Mofenson *et al.*⁶⁰ employed both alkaline diuresis and repeat dose activated charcoal in three adolescents and found a mean elimination half-life of 12.3 ± 1.3 hours during treatment.

The clearance of barbiturate with peritoneal dialysis rarely exceeds 10 ml/minute^{112,113} which is unimpressive compared with clearance values of 60 ml/minute with haemodialysis^{114,115} and of 77 ml/minute with haemoperfusion;⁵⁹ values achieved by repeat dose charcoal therapy are of the order of 84 ml/minute.¹¹¹

Carbamazepine poisoning In a randomized cross-over study³⁴ in five volunteers given 400 mg carbamazepine orally, the elimination half-life was reduced from 32 to 17.6 hours following repeat dose charcoal therapy. Boldy *et al.*¹¹⁶ have shown in 15 poisoned patients that charcoal therapy increases carbamazepine clearance (body clearance 113 ± 44 ml/minute; plasma half-life 8.6 ± 2.4 hours) when compared to similarly intoxicated cases^{117–119} treated with supportive measures alone (mean half-life 19.0 ± 6.9 hour). Charcoal haemoperfusion has been shown to produce clearance values of 80–129 ml/minute^{120–122} and elimination half-lives during perfusion of 8.6–10.7 hours,¹²³ though these values are similar to those achieved by repeat dose activated charcoal therapy.¹¹⁶

Phenytoin Although there is experimental evidence¹²³ that phenytoin clearance may be increased from 5 to 20 ml/minute by forced diuresis this is less impressive than the values achieved by body clearance alone.¹²⁴ The value of repeat dose activated charcoal has been evaluated in one case and appears to increase phenytoin elimination.¹²⁵

Ethchlorvynol poisoning Mean clearance values of 18.5 ml/minute and 64 ml/minute were found in one study during peritoneal and haemodialysis respectively;¹²⁶ resin haemoperfusion is superior to haemodialysis.¹²⁷

Glutethimide poisoning Peritoneal dialysis and haemodialysis are unimpressive and produce clearance values of only 17 ml/minute¹²⁸ and 34–63 ml/minute,¹²⁹ respectively, though higher values have been reported occasionally.¹²⁸ Haemoperfusion^{130,131} results in a more impressive drug clearance than haemodialysis though a significant rebound in plasma concentration occurs in some patients and repeated haemoperfusion may be necessary.

Intoxication due to trichloroethanol derivatives Chloral hydrate is metabolized to trichloroethanol and trichloroacetic acid. There are no data on the efficacy of peritoneal dialysis but clearances of 120–162 ml/minute have been achieved during haemodialysis.^{132,133} Mean haemoperfusion clearances of 198 ± 20 ml/minute were achieved by De Groot¹³⁴ and, hence, haemoperfusion is more effective than haemodialysis in removing trichloroethanol.

Meprobamate poisoning Repeat dose activated charcoal appears to reduce the elimination half-life of meprobamate.¹³⁵ Mouton *et al.*¹³⁶ have reported that peritoneal dialysis will produce a maximum clearance of only 27 ml/minute, whereas clearances as high as 62 ml/minute have been found with haemodialysis.¹³⁷ Clearance values of 80–300 ml/minute have been achieved using charcoal and resin haemoperfusion with very high blood flow rates.¹³⁴

Tricyclic antidepressant poisoning A variable effect of activated charcoal has been reported on the elimination of tricyclic antidepressants. In volunteer studies, plasma half-lives of amitriptyline and doxepin but not of imipramine^{138–140} were reduced. Recently, a beneficial effect of activated charcoal has been claimed in three patients poisoned with dothiepin.¹⁴¹ It is unlikely, though, that any clinical useful reduction in the elimination half-life of these drugs will be achieved because of their very large volume of distribution.

Diazepam poisoning The elimination half-life of diazepam was reduced from 195 to 18 hours as a result of charcoal administration in a patient with liver disease treated for delirium tremens with intravenous phenobarbitone and diazepam.¹⁴² Except in such special circumstances, treatment other than supportive measures is unlikely to be required for benzodiazepine poisoning. If it is, the use of the specific antagonist, flumazenil, will provide immediate resuscitation.

Ethanol poisoning A dialysate clearance of 10–20 ml/minute was achieved during peritoneal dialysis in a patient who presented with a blood ethanol concentration of 15,000 mg/l and survived.¹⁴³ Haemodialysis is the preferred elimination technique in that it is more efficient than both peritoneal dialysis and charcoal haemoperfusion and it should be considered in a severely intoxicated patient if the blood ethanol concentration is > 500 mg/l and/or if severe metabolic acidosis is present.

Methanol poisoning During experimental methanol intoxication in dogs, the spontaneous half-life of over 70 hours was reduced by a factor of 10 with

peritoneal dialysis.¹⁴⁴ Peritoneal dialysis removed three times as much methanol as renal excretion and haemodialysis about 25 times more.¹⁴⁴ Keyvan-Larijani and Tannenbergs¹⁴⁵ reported the value of peritoneal dialysis in three patients with admission blood methanol concentrations ranging from 960 to 1,980 mg/l. After 8 hours, a 13% reduction in methanol concentration was achieved compared with a 66% reduction by haemodialysis in other patients. One death and one case of permanent blindness occurred in those treated by peritoneal dialysis whereas all patients treated by haemodialysis survived.

Due to its low molecular weight (32 daltons), lack of protein-binding and low volume of distribution (0.7 litres/kg), methanol is easily removed by haemodialysis.¹⁴⁶ The clearance values lie between 150 and 200 ml/minute depending on the blood flow and surface area of the dialyser. In addition, haemodialysis may also remove formate;^{147,148} clearance values range from 140 to 150 ml/minute.

Ethylene glycol poisoning Vale *et al.*¹⁴⁹ showed that peritoneal dialysis removes ethylene glycol, albeit at a slower rate than haemodialysis. Since ethylene glycol has a low molecular weight (62 daltons), low protein-binding and a volume of distribution of 0.7–0.8 litres/kg, this glycol should be haemodialysable on theoretical grounds though it is less so than methanol.^{150–152} Recently, the dialysance of glycolate (140 ml/minute), a metabolite of ethylene glycol, has also been demonstrated in one patient.¹⁵³

Isopropanol poisoning Isopropanol has a small molecular weight, low volume of distribution and low plasma protein binding and dialysis is therefore likely to be of benefit. Peritoneal dialysis is considerably less effective than haemodialysis, both in removing isopropanol and in shortening the duration of coma in those intoxicated.^{154–158}

Phenoxyacetate herbicide poisoning Alkaline diuresis greatly increases the renal clearance of 2,4-dichlorophenoxyacetic acid (2,4-D) with a concomitant rapid fall in plasma concentration (half-life of 3.7 hours compared to 143 hours) and corresponding clinical improvement.¹⁵⁹ The effect on mecoprop was similar but less dramatic.¹⁵⁹ These workers showed that, with alkaline diuresis the renal clearance of 2,4-D rose from 0.14 ml/minute to 63 ml/minute and that for each increase of 1 pH unit, the renal clearance of 2,4-D rose almost fivefold. In the case of mecoprop, the renal clearance increased twofold for each 1 unit pH rise. More recent evidence¹⁶⁰ confirms the value of alkaline diuresis, not only in the case of 2,4-D and mecoprop, but also in the case of dichlorprop.

Phencyclidine poisoning Done¹⁶¹ showed that acid diuresis increases urinary clearance of phencyclidine from 36 to 271 ml/minute, but, surprisingly, there was little effect either on plasma concentration or the time to clinical recovery. Moreover, acid diuresis may potentiate the toxicity of phencyclidine by increasing the risk of renal failure secondary to rhabdomyolysis. Activated charcoal may adsorb phencyclidine and, as this drug is known to diffuse back into the gut after absorption,¹⁶¹ repeat dose charcoal may be an appropriate alternative.

Dapsone poisoning Neuvonen *et al.*^{162,163} have demonstrated a reduction in the elimination half-life of dapsone after repeat doses of activated charcoal in both volunteers and three poisoned patients.

Conclusion

Repeat dose activated charcoal has been shown to enhance the non-renal elimination of phenobarbi-

tone, carbamazepine, phenytoin, theophylline, salicylate, dapsone, diazepam, digitoxin, digoxin, meprobamate, phenylbutazone and cyclosporin. As yet, because of the difficulty in conducting large clinical trials, repeat-dose charcoal therapy has not been shown to effect a reduction in either the morbidity and mortality in patients poisoned with these drugs. Further studies are therefore required to establish the role of this treatment and to define the optimum doses of activated charcoal that should be administered.

Haemodialysis is an efficient technique for the removal of salicylate, ethanol, methanol, ethylene glycol, isopropanol and lithium; peritoneal dialysis is generally less efficient for these indications. Haemoperfusion is of particular value in severely poisoned patients who have ingested a barbiturate (with the possible exception of phenobarbitone) or non-barbiturate hypnotic, theophylline, disopyramide, or phenylbutazone and who have failed to improve despite the use of supportive measures and activated charcoal.

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Reducing absorption

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