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Position Statement and Practice Guidelines on the Use of Multi-Dose Activated Charcoal in the Treatment of Acute Poisoning

American Academy of Clinical Toxicology, European Association of Poisons Centres and Clinical Toxicologists

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Position Statement and Practice Guidelines on the Use of Multi-Dose Activated Charcoal in the Treatment of Acute Poisoning

American Academy of Clinical Toxicology;
European Association of Poisons Centres
and Clinical Toxicologists

ABSTRACT

In preparing this Position Statement, all relevant scientific literature was identified and reviewed critically by acknowledged experts using agreed criteria.[1–124] Well-conducted clinical and experimental studies were given precedence over anecdotal case reports and abstracts were not usually considered. A draft Position Statement was then produced and subjected to detailed peer review by an international group of clinical toxicologists chosen by the American Academy of Clinical Toxicology and the European Association of Poisons Centres and Clinical Toxicologists. The Position Statement went through multiple drafts before being approved by the Boards of the two societies.

The Position Statement includes a summary statement for ease of use and is supported by detailed documentation which describes the scientific evidence on which the Statement is based.

Although many studies in animals and volunteers have demonstrated that multiple-dose activated charcoal increases drug elimination significantly, this therapy has not yet been shown in a controlled study in poisoned patients to reduce morbidity and mortality. Further studies are required to establish its role and the optimal dosage regimen of charcoal to be administered.

Based on experimental and clinical studies, multiple-dose activated charcoal should be considered only if a patient has ingested a life-threatening amount of carbamazepine, dapsone, phenobarbital, quinine, or theophylline. With all

This Position Statement is endorsed by the Canadian Association of Poison Control Centres.

of these drugs there are data to confirm enhanced elimination, though no controlled studies have demonstrated clinical benefit.

Although volunteer studies have demonstrated that multiple-dose activated charcoal increases the elimination of amitriptyline, dextropropoxyphene, digitoxin, digoxin, disopyramide, nadolol, phenylbutazone, phenytoin, piroxicam, and sotalol, there are insufficient clinical data to support or exclude the use of this therapy.

The use of multiple-dose charcoal in salicylate poisoning is controversial. One animal study and 2 of 4 volunteer studies did not demonstrate increased salicylate clearance with multiple-dose charcoal therapy. Data in poisoned patients are insufficient presently to recommend the use of multiple-dose charcoal therapy for salicylate poisoning.

Multiple-dose activated charcoal did not increase the elimination of astemizole, chlorpropamide, doxepin, imipramine, meprobamate, methotrexate, phenytoin, sodium valproate, tobramycin, and vancomycin in experimental and/or clinical studies.

Unless a patient has an intact or protected airway, the administration of multiple-dose activated charcoal is contraindicated. It should not be used in the presence of an intestinal obstruction. The need for concurrent administration of cathartics remains unproven and is not recommended. In particular, cathartics should not be administered to young children because of the propensity of laxatives to cause fluid and electrolyte imbalance.

In conclusion, based on experimental and clinical studies, multiple-dose activated charcoal should be considered only if a patient has ingested a life-threatening amount of carbamazepine, dapsone, phenobarbital, quinine, or theophylline.

This Position Statement was drafted by JA Vale, EP Krenzelok, and GD Barceloux.

SUMMARY STATEMENT

INTRODUCTION

- The challenge for clinicians managing poisoned patients is to identify at an early stage those who are most at risk of developing serious complications and who might potentially benefit, therefore, from elimination techniques.
- Multiple-dose activated charcoal therapy involves the repeated administration (more than 2 doses) of oral activated charcoal to enhance the elimination of drugs already absorbed into the body.
- No evidence has yet been published to demonstrate convincingly that multiple-dose activated charcoal reduces morbidity and mortality in poisoned patients.
- Further studies are required to establish its role and the optimal dosage regimen of charcoal to be administered.

RATIONALE

- Drugs with a prolonged elimination half-life following overdose and small volume of distribution (<1 L/kg body weight), are particularly likely to have their elimination enhanced to a clinically significant degree by multiple-dose activated charcoal.
- Multiple-dose activated charcoal is thought to produce its beneficial effect by interrupting the enteroenteric and, in some cases, the enterohepatic and the enterogastric circulation of drugs. In addition, any unabsorbed drug still present in the gut will

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be adsorbed to activated charcoal, thereby reducing drug absorption.

ANIMAL STUDIES

- In animal studies multiple-dose activated charcoal has been shown to reduce the elimination half-life and increase the total body clearance of acetaminophen (paracetamol),[1] digoxin,[1] phenobarbital,[2] phenytoin,[3] and theophylline.[1] The elimination of salicylate[4] and valproic acid[1] was not enhanced by this means.

VOLUNTEER STUDIES

- Studies in volunteers have demonstrated that multiple-dose activated charcoal increases the elimination of carbamazepine,[5] dapsone,[6] dextropropoxyphene,[7] digitoxin,[8,9] digoxin,[8–10] disopyramide,[11] nadolol,[12] phenobarbital,[5,13–15] phenylbutazone,[5] phenytoin,[16,17] piroxicam,[18] quinine,[19] sotalol,[20] and theophylline.[21–26]
- The elimination of salicylate was increased by multiple-dose activated charcoal in two studies,[27,28] but not in two other studies.[29,30] Although a statistically significant difference was shown, the treatment effect was small.
- Multiple-dose activated charcoal therapy did not increase the elimination of astemizole,[31] chlorpropamide,[32] sodium valproate,[33] tobramycin[34,35] and vancomycin.[36]
- The elimination half-life of amitriptyline,[37] but not of doxepin[38] or imipramine,[39] was also reduced by multiple-dose activated charcoal in volunteer studies. Crome *et al*.[40] showed a significant reduction in the area under the curve (AUC) of nortriptyline after multiple-dose activated charcoal. However, there are good pharmacokinetic reasons to suggest that in the case of tricyclic antidepressants, a clinically-significant increase in body clearance is unlikely to result from the use of such treatment, even though the apparent half-life may be shortened.

CLINICAL STUDIES

- Clinical studies of multiple-dose activated charcoal consist only of case series and reports.
- Studies in poisoned patients have confirmed those studies in volunteers which demonstrate that the elimination of carbamazepine,[41,42] dapsone,[6,43] phenobarbital,[44–47] quinine,[48] and theophylline[23,26,49–55] is enhanced by multiple-dose activated charcoal.
- Clearance values achieved by multiple-dose activated charcoal in the case of carbamazepine,[89–91] dapsone,[43] and phenobarbital[96,96] are comparable to those produced by the more invasive techniques of hemodialysis and hemoperfusion.
- There is also some evidence to suggest that, contrary to the findings in 1 animal[4] and 2 volunteer studies,[29,30] multiple-dose activated charcoal may increase the elimination of salicylate[56,57]; these results need to be confirmed in further studies before this therapy can be recommended.
- Although the elimination of digoxin was enhanced by the use of multiple-dose activated charcoal in 4 experimental studies,[1,8,9,10] in 3 case reports,[58–60] and 1 case series,[61] it is unlikely that the increase in body clearance of digoxin will be of clinical significance because of the large volume of distribution of digoxin. Moreover, severe digoxin poisoning may be treated effectively with digoxin-specific antibody fragments. There is also limited clinical evidence that multiple-dose activated charcoal may increase the clearance of digitoxin.[62]
- The elimination of dapsone was increased by multiple-dose activated charcoal in volunteer and clinical studies.[6,43]
- Although an experimental study[36] did not demonstrate enhanced clearance, 2 case reports[63,64] suggest that multiple-dose activated charcoal may increase vancomycin clearance.
- Multiple-dose activated charcoal does not appear to increase the clearance of meprobamate,[65,66] methotrexate,[67] phenytoin,[68–72] tricyclic antidepressants,[73,74] and valproic acid[75] in patients who have ingested or been administered these drugs.

INDICATIONS

- The use of multiple-dose activated charcoal should be considered if the patient has ingested a life-threatening amount of carbamazepine, dapsone, phenobarbital, quinine, or theophylline, and may obviate the need for invasive extracorporeal techniques in these cases.
- The ultimate decision to use multiple-dose activated charcoal therapy depends on:
  (a) the physician's clinical judgment regarding

the expected outcome in a patient poisoned with carbamazepine, dapsone, phenobarbital, quinine, or theophylline;

(b) the presence of a contraindication to the use of activated charcoal therapy;

(c) the effectiveness of alternative methods of treatment.

DOSAGE REGIMEN

- The optimum dose of charcoal is unknown but it is recommended that after an initial dose of 50–100 g to an adult, activated charcoal should be administered at a rate of not less than 12.5 g/h or equivalent. Lower doses (10–25 g) of activated charcoal may be employed in children less than 5 years of age as usually they have ingested smaller overdoses and their gut lumen capacity is smaller.
- Activated charcoal should be continued until the patient's condition and laboratory parameters, including plasma drug concentration, are improving.
- It may be difficult in clinical practice to administer substantial doses of activated charcoal because of drug-induced vomiting such as occurs with theophylline in overdose. Smaller doses (and therefore smaller volumes) of activated charcoal administered more frequently may reduce the likelihood of vomiting. However, it is often necessary to give an antiemetic intravenously to ensure satisfactory administration of charcoal, even by a nasogastric tube.

CO-ADMINISTRATION OF A CATHARTIC

- The need for concurrent administration of a cathartic, such as sorbitol, remains unproven and is not recommended. In particular, a cathartic should not be administered to young children because of the propensity to cause fluid and electrolyte imbalance.

CONTRAINDICATIONS

Absolute

- An unprotected airway
- Presence of intestinal obstruction
- A gastrointestinal tract not anatomically intact

Relative

- Decreased peristalsis (decreased bowel sounds, abdominal distension, ileus) such as occurs following overdoses of drugs with opioid or anticholinergic properties.
- Multiple-dose charcoal should be administered cautiously in the presence of decreased peristalsis with careful monitoring for the development of obstruction and for the prevention of aspiration.

COMPLICATIONS OF USE

- Treatment with multiple-dose activated charcoal is relatively free from serious side-effects, although transient constipation may occur if aqueous charcoal is administered in substantial dose, particularly in nonambulatory patients due to a depressed level of consciousness.
- Occasionally, bowel obstruction has been reported necessitating manual evacuation or surgical intervention.[107,108,110,111]
- Regurgitation, with subsequent aspiration into the lungs of gastric contents containing charcoal, or direct installation of charcoal into the lungs as a result of a misplaced nasogastric tube, has led rarely to severe pulmonary complications and death.[112,117–119] Emesis of aqueous activated charcoal occurs infrequently. The incidence appears to be greater when activated charcoal is administered with sorbitol.

SUPPORTING DOCUMENTATION

INTRODUCTION

Charcoal is prepared from vegetable matter, usually peat, coal, wood, coconut shell, or petroleum. Charcoal is ''activated'' by heating it at high temperature in a stream of oxidizing gas (e.g., steam, carbon dioxide, air) or with an activating agent, such as phosphoric acid or zinc chloride, or by a combination of both. The process of activation creates a highly developed internal pore structure and thereby increases the surface area from 2–4 m^2/g to an area in excess of 1500 m^2/g. Medicinal activated charcoal must meet BP, USP, or similar standards and have a surface area of at least 900 m^2/g.

Multiple-dose activated charcoal therapy is the repeated administration (more than 2 doses) of oral acti-

vated charcoal with the intent of enhancing drug elimination.

Multiple-dose activated charcoal is perceived as a simple, inexpensive, and safe therapy which may avoid the need for more invasive procedures such as hemodialysis and hemoperfusion. While studies in volunteers demonstrate that its administration both reduces the elimination half-life and increases drug clearance of some drugs, most of the clinical data supporting the use of multiple-dose activated charcoal are anecdotal case reports. Controlled clinical studies are necessary to establish the role of this therapy.

METHODOLOGY

In preparing this Position Statement all relevant scientific literature was identified by searching Medline, Toxline, and EMBASE using the terms ''activated charcoal,'' ''multiple-dose activated charcoal,'' and ''repeat dose activated charcoal.'' The original papers were obtained and reviewed critically by a group of clinical toxicologists chosen by the 2 sponsoring Societies. A draft Position Statement was produced which went through multiple drafts before being approved by the Boards of the two Societies.

RATIONALE

Drugs with a prolonged elimination half-life following overdose are likely to have their elimination enhanced by multiple-dose activated charcoal.[1,76] Other relevant pharmacokinetic factors include volume of distribution (<1 L/kg body weight), pKa, and protein binding. If multiple-dose activated charcoal therapy is initiated during a drug's distributive phase, particularly if it is long, it may have a considerable pharmacokinetic effect by interrupting drug distribution into tissues.[1] In addition, if a major route of elimination is no longer available due to the onset of organ failure, this treatment has the potential to make a contribution to total body clearance of the drug ingested which is clinically beneficial.

MECHANISMS OF ACTION

Multiple-dose activated charcoal is thought to produce its beneficial effects by:

1. Binding any drug which diffuses from the circulation into the gut lumen.[77] After absorption, a drug will reenter 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. Under these ''sink'' conditions, a concentration gradient is maintained and the drug passes continuously into the gut lumen where it is adsorbed to charcoal. This process has been termed ''gastrointestinal dialysis.''[78] Animal studies have confirmed that activated charcoal significantly interrupts the enteroenteric circulation of phenobarbital.[79]
2. Interrupting the enterohepatic and the enterogastric circulation of drugs.

ANIMAL STUDIES

Acetaminophen (Paracetamol). Acetaminophen 30 mg/kg was administered intravenously over 12 minutes with 3 other drugs (aminophylline, digoxin, valproic acid) to 7 pigs with an indwelling gastrostomy tube.[1] Activated charcoal 25 g with sorbitol (48 g) was administered as the initial intervention at time zero and an aqueous slurry of activated charcoal (25 g) was administered at 2, 4, 6, 12, 18, 24, and 30 hours via the gastrostomy tube. The mean acetaminophen half-life was reduced significantly ($p < 0.01$) from 1.7 ± (SD) 0.2 hours to 1.4 ± 0.3 hours and significantly increased ($p < 0.01$) the clearance from 4.57 ± 0.54 mL/min/kg to 5.41 ± 0.63 mL/min/kg.

Aspirin. In a crossover study, 6 fasted pigs received aspirin 300 mg/kg intravenously followed by no treatment or activated charcoal 1 g/kg every hour for 6 doses [the first dose contained sorbitol (70%) 4 mL/kg] via a gastrostomy tube.[4] There were no statistical differences between the control and treatment arms. Mean peak serum salicylate concentrations were 474 ± 62 mg/L and 484 ± 3.9 mg/L, respectively ($p = 0.74$), and the AUC over 6 hours was 171,000 ± 24,000 mg · min/L in the control group and 188,000 ± 18,000 mg · min/L in the treatment group ($p = 0.22$).

Digoxin. Seven female pigs were administered digoxin 30 μg/kg intravenously together with 3 other drugs (aminophylline, digoxin, valproic acid).[1] Activated charcoal (25 g) with sorbitol (48 g) was administered as the initial intervention at time zero and an aqueous slurry of activated charcoal (25 g) was administered at 2, 4, 6, 12, 18, 24, and 30 hours via an indwelling gastrostomy tube. The half-life was reduced significantly ($p < 0.001$) from a mean of 64.8 ± (SD) 23.7 hours to 17.2 ± 5.6 hours.

Clearance was increased from 2.33 ± 0.85 mL/min/kg to 7.05 ± 1.42 mL/min/kg ($p < 0.001$).

Phenobarbital (Phenobarbitone). Arimori and Nakano[2] administered phenobarbital 10 mg/kg body weight intravenously to 5 fasted Wistar strain male rats. Activated charcoal 300 mg was given orally at time zero and then in a dose of 150 mg at 1, 2, 3, 4, and 6 hours after dosing. The mean phenobarbital elimination half-life was reduced significantly ($p < 0.05$) from 8.52 ± (SEM) 0.62 hours to 5.71 ± 0.35 hours and the mean total body clearance of phenobarbital was increased significantly ($p < 0.01$) from 50.2 ± (SEM) 2.73 mL/kg/h to 77.0 ± 1.21 mL/kg/h. There was a significant ($p < 0.01$) reduction in the mean AUC of 64% from 184.2 ± 9.56 mcg · h/mL to 118.7 ± 188 mcg · h/mL.

Phenytoin. A reduction in the elimination half-life of phenytoin by multiple-dose activated charcoal was reported by Arimori and Nakano.[3] Five fasted Wistar strain rats were treated with activated charcoal 300 mg at time zero and 150 mg at 1, 2, 3, 4, and 6 hours after the administration of a single intravenous dose of phenytoin 10 mg/kg or 50 mg/kg body weight. There were no statistical differences between any parameters at 10 mg/kg. The mean elimination half-life at the 50 mg/kg dose fell significantly ($p < 0.05$) from 6.2 ± (SEM) 0.73 hours to 4.77 ± 0.43 hours and the total body clearance increased significantly ($p < 0.01$) from 0.16 ± (SEM) 0.01 L/kg/h to 0.22 ± 0.01 L/kg/h. The AUC was reduced significantly ($p < 0.01$) from 311.2 ± 19.3 mcg · h/mL to 233.5 ± 12.4 mcg · h/mL.

Theophylline. Arimori and Nakano[2] administered aminophylline 10 mg/kg body weight intravenously to 5 fasted Wistar strain rats. Activated charcoal 300 mg was given orally at time zero and then 150 mg was administered at 1, 2, 3, and 4 hours postdosing with aminophylline. The mean elimination half-life was reduced significantly ($p < 0.05$) from 4.63 ± (SEM) 0.49 hours to 2.84 ± 0.20 hours and the mean total body clearance of theophylline was increased significantly ($p < 0.05$) from 66.7 ± (SEM) 9.03 mL/kg/hour to 101.2 ± 9.77 mL/kg/h. There was a significant ($p < 0.02$) reduction in the mean AUC from 138.1 ± 17.5 mcg · h/mL to 88.0 ± 8.39 mcg · h/mL.

Aminophylline was administered intravenously to 5 dogs in doses of 50–100 mg/kg followed by duodenal administration of activated charcoal 45–50 g every hour for 7 hours (8 doses).[80] Although mean AUC values were reduced in the charcoal-treated group, no statistical analysis was undertaken and the results are therefore uninterpretable.

Chyka *et al*.[1] administered theophylline (as aminophylline) 8.9 mg/kg intravenously over 12 minutes to 7 pigs that were also coadministered digoxin, acetaminophen, and valproic acid. Activated charcoal (25 g) with sorbitol (48 g) was administered as the initial intervention at time zero and an aqueous slurry of activated charcoal (25 g) was administered at 2, 4, 6, 12, 18, 24, and 30 hours via a gastrostomy tube after the initiation of the aminophylline infusion. The mean (±SD) theophylline half-life was reduced from 9.4 ± 2.0 to 3.5 ± 2.3 ($p < 0.01$) hours and the AUC from 168.9 ± 34.3 mg/h/L to 43.6 ± 9.8 mg/h/L ($p < 0.001$).

Valproic acid. Valproic acid was administered intravenously over 12 minutes with 3 other drugs (acetaminophen, aminophylline, digoxin) to 7 pigs with an indwelling gastrostomy tube.[1] Activated charcoal (25 g) with sorbitol (48 g) was administered as the initial intervention at time zero and an aqueous slurry of activated charcoal (25 g) was administered at 2, 4, 6, 12, 18, 24, and 30 hours via the gastrostomy tube, but did not reduce significantly the half-life and AUC or increase the clearance of valproic acid.

VOLUNTEER STUDIES

Aspirin. Barone *et al*.[27] gave activated charcoal 50 g to 10 fasted volunteers at 1, 5, and 9 hours after the administration of aspirin 1944 mg. There was a statistically significant reduction ($p < 0.01$) in the mean % recovery of total salicylate from the urine (49.2 ± 12.48%) compared to controls [91.0 ± (SD) 6.12%]; serum salicylate concentrations were not measured.

Kirshenbaum *et al*.[28] investigated the effect of multiple-dose charcoal therapy in 10 volunteers who were given aspirin 2880 mg (29–59 mg/kg body weight) orally which produced a mean peak serum salicylate concentration of 192 ± (SD) 27.6 mg/L. During the treatment phase, between 4 and 10 hours postingestion, each received activated charcoal 25 g every 2 hours (total dose 100 g). A significant reduction ($p < 0.05$) in the AUC of 9% was observed in the treatment phase, with an 18% reduction ($p < 0.01$) in total urinary excretion of salicylate. While concluding that the ''modest'' effect of multiple-dose charcoal on salicylate clearance suggested it was ''of questionable value'' in the treatment of acute salicylate poisoning, the authors acknowledged that the observed benefit would be potentially greater in severely intoxicated patients in whom the plasma concentrations would be significantly higher and the salicylate half-life substantially longer than in this study.

The administration of activated charcoal 25 g 4 hours

after aspirin dosing (1300 mg orally) to 6 fasted adult volunteers, followed by 3 further doses of charcoal 10 g every 2 hours, did not result in a significant reduction in half-life or AUC.[29] Peak serum salicylate concentrations ranged from 55–136 mg/L.

Mayer *et al*.[30] administered aspirin 2880 mg (33–44 mg/kg body weight) to 9 volunteers and 4 hours later activated charcoal 25 g was given and repeated every 2 hours for 4 doses. Following charcoal treatment, no significant difference was observed in the mean peak serum salicylate concentrations: 160 ± (SD) 17 mg/L in the control group and 150 ± 24 mg/L in the charcoal group. No significant differences in the AUCs were observed.

Astemizole. Laine *et al*.[31] demonstrated that activated charcoal (12 g) administered twice daily (from 6 hours onwards) to 7 volunteers for 8 days did not alter the rate of elimination or AUC (0–192 hours) of astemizole (30 mg).

Carbamazepine. In a randomized crossover study in 5 fasted volunteers given carbamazepine 400 mg orally, Neuvonen and Elonen[5] found the mean elimination half-life was reduced significantly ($p < 0.05$) from 32 ± (SEM) 3.4 hours to 17.6 ± 2.4 hours following multiple-dose charcoal therapy (50 g at 10 hours postdosing; 17 g at 14, 24, 36, and 48 hours postdosing). The mean total body clearance was also increased significantly ($p < 0.05$) from 22.0 ± (SEM) 1.9 mL/min to 40.0 ± 2.7 mL/min.

Chlorpropamide. Neuvonen and Kärkkäinen[32] demonstrated that the half-life of chlorpropamide was not reduced significantly by the use of multiple-dose activated charcoal (50 g at 6 hours followed by 12.5 g every 6 hours for 8 hours) following the administration of chlorpropamide 250 mg orally to 6 volunteers.

Dapsone. Neuvonen *et al*.[6] administered dapsone 500 mg to 5 volunteers over 4 days (100 mg daily for 3 days and 100 mg twice daily on day 4) in a randomized crossover study. Ten hours after the last dose, subjects were given charcoal 50 g, then 17 g every 12 hours for an additional 4 doses. The dapsone elimination half-life was reduced significantly ($p < 0.01$) from 20.5 ± (SEM) 2.0 hours during the control period to 10.8 ± 0.4 hours after charcoal. The half-life of the metabolite monoacetyldapsone was also reduced significantly ($p < 0.001$) during treatment.

Dextropropoxyphene. Kärkkäinen and Neuvonen[7] found that the elimination half-lives of dextropropoxyphene and its metabolite, norpropoxyphene, were reduced in 6 volunteers given activated charcoal 50 g 6 hours after the oral administration of dextropropoxyphene 130 mg; further doses of charcoal (12.5 g) were administered every 6 hours for 8 doses. It should be noted that in the control phase, volunteers received activated charcoal 50 g 5 minutes after dextropropoxyphene dosing. The mean elimination half-life of dextropropoxyphene was reduced significantly ($p < 0.05$) from 31.1 ± (SEM) 4.2 hours to 21.2 ± 3.1 hours and the mean elimination half-life of norpropoxyphene was reduced significantly ($p < 0.001$) from 34.4 ± (SEM) 2.5 hours to 19.8 ± 3.4 hours.

Digitoxin and digoxin. Park *et al*.[8] gave 6 adult volunteers intravenous infusions of digoxin (0.75 mg/70 kg body weight) or digitoxin (1 mg/70 kg body weight) followed either by water alone or activated charcoal (20 g immediately, then 20 g every 4 hours for 36 hours; a further 20 g dose was administered 48 hours postinfusion). The serum digoxin half-life was decreased significantly ($p < 0.05$) from 23.1 ± (SEM) 1.7 hours to 17.0 ± 1.5 hours but the increase in digoxin clearance was not statistically significant ($p > 0.1$). The half-life of digitoxin was decreased significantly ($p < 0.01$) from 110.6 ± 11.0 hours to 51.1 ± 4.5 hours and digitoxin clearance was increased significantly ($p < 0.001$) from 0.24 ± 0.01 to 0.47 ± 0.04 L/h. The authors also reported a reduction in the digoxin elimination half-life from 93.3 to 29.3 hours in a volunteer with chronic renal failure; the total body clearance of digoxin increased from 3.6 L/h to 10.1 L/h.

Reissell and Manninen[9] found that during maintenance therapy with digoxin or digitoxin in 6 individuals aged 60–74 years, the administration of activated charcoal 6 g a day significantly decreased ($p < 0.001$) the mean plasma digoxin concentration by 31.2% and reduced significantly ($p < 0.05$) the mean serum digitoxin concentration by 18.3%.

Activated charcoal (225 g over 40 hours) was given to 10 healthy volunteers after the intravenous administration of digoxin 10 μg/kg. Charcoal increased significantly ($p < 0.005$) the total body clearance of digoxin from 12.2 ± (SD) 2.0 L/h to 18.0 ± 2.9 L/h and the terminal half-life was reduced significantly ($p < 0.005$) from 36.5 ± (SD) 11.8 hours to 21.5 ± 6.5 hours.[10]

Disopyramide. Arimori *et al*.[11] administered activated charcoal (40 g at 4 hours and 20 g at 6, 8, and 12 hours) to 6 volunteers after they had been given disopyramide 200 mg orally. The mean elimination half-life was decreased significantly ($p < 0.05$) from 6.09 ± (SEM) 0.48 hours to 4.11 ± 0.45 hours and the total body clearance increased significantly ($p < 0.01$) from 0.113 ± (SEM) 0.017 L/h/kg to 0.138 ± 0.019 L/h/kg.

Nadolol. The elimination half-life of oral nadolol 80 mg in 8 adult volunteers was reduced significantly ($p <$

0.05) from 17.3 ± (SEM) 1.7 hours to 11.8 ± 1.6 hours by small doses (500 mg at 3 and 4 hours after dosing and then 250 mg hourly for a further 8 hours) of activated charcoal tablets.[12]

Phenobarbital (Phenobarbitone). Neuvonen and Elonen[5] gave 5 fasted volunteers activated charcoal 50 g at 10 hours and 17 g at 24, 36, and 48 hours after the oral administration of phenobarbital 200 mg and found that the mean phenobarbital elimination half-life was reduced significantly ($p < 0.05$) from 110 ± (SEM) 23 hours to 19.8 ± 1.0 hours. The total phenobarbital clearance was increased significantly ($p < 0.05$) from 4.6 ± (SEM) 0.9 mL/min to 23.0 ± 3.0 mL/min.

Six volunteers were given activated charcoal 40 g at time zero and 20 g at 6, 12, 18, 24, 30, 42, and 66 hours following the intravenous administration of phenobarbital 200 mg.[13] The mean phenobarbital half-life was reduced significantly ($p < 0.01$) from 110 ± (SEM) 8 hours to 45 ± 6 hours, the mean total body clearance of phenobarbital was increased significantly ($p < 0.01$) from 4.4 ± 0.2 to 12.0 ± 1.6 mL/kg/h, and the nonrenal clearance of phenobarbital was increased from 52 to 80% of the total body clearance.

In another study[14] the effects of charcoal alone and a charcoal-sorbitol mixture on phenobarbital elimination were investigated in 6 men. Following the intravenous administration of phenobarbital 200 mg/70 kg over 1 hour, either activated charcoal 105 g or activated charcoal 105 g with sorbitol was given over a 36-hour period (30 g at end of dosing; 15 g at 6, 12, 18, 24, and 36 hours after dosing). The mean phenobarbital elimination half-life ($T_{1/2\,3–60h}$) fell significantly ($p < 0.05$) from 72 ± (SD) 7 hours (control) to 36 ± 4 hours (charcoal alone), and 30 ± 4 hours (charcoal-sorbitol). However, there was no significant difference in the terminal elimination half-life in each group: 102 ± 19 hours (control), 119 ± 22 hours (charcoal alone), and 116 ± 25 hours (charcoal-sorbitol). The apparent mean systemic clearance of phenobarbital increased significantly (but no p value was included) from 0.0895 ± 0.019 mL/min (control) to 0.141 ± 0.029 mL/min/kg (charcoal alone) and 0.146 ± 0.036 mL/min/kg (charcoal-sorbitol).

Frenia *et al*.[15] administered phenobarbital 5 mg/kg to 10 volunteers. Each volunteer received 6 doses of activated charcoal: 50 g with sorbitol (50 g of 70%) 30 minutes after phenobarbital and five 25 g doses at 4.5, 8.5, 12.5, 16.5, and 20.5 hours; and a dose of sorbitol (25 g of 70%) was administered at 12.5 and 24.5 hours. The mean (±SD) phenobarbital half-life was reduced significantly ($p = 0.005$) from 148.1 ± 332.1 hours to 18.87 ± 14.70 hours and the mean (±SD) phenobarbital clearance was increased significantly ($p < 0.0005$) from 2.79 ± 9.69 mL/kg/h (control group) to 19.95 ± 11.5 mL/kg/h (charcoal group).

Phenylbutazone. Multiple-dose activated charcoal (50 g 10 hours postdosing; 17 g at 14, 24, 36, and 48 hours postdosing) reduced significantly ($p < 0.05$) the mean elimination half-life of phenylbutazone from 51.5 ± (SEM) 7.6 hours to 36.7 ± 4.1 hours after the oral administration of phenylbutazone 200 mg.[5] The total phenylbutazone clearance was also increased significantly ($p < 0.05$) from 1.5 ± (SEM) 0.16 mL/min to 2.1 ± 0.23 mL/min.

Phenytoin. The effect of multiple-dose activated charcoal on the elimination of intravenously administered phenytoin was studied in 7 fasting volunteers by Mauro *et al*.[16] Each participant received phenytoin 15 mg/kg intravenously over 60 minutes which produced a mean C_{max} of approximately 22 mg/L. At the end of the phenytoin infusion, activated charcoal 60 g with sorbitol was given followed by 30 g (with random sobitol administration) at 2, 4, 8, 12, 24, 30, 36, and 48 hours (total dose 300 g over 48 hours). Charcoal significantly reduced ($p < 0.001$) the mean phenytoin elimination half-life from 44.5 ± (SD) 14.0 hours to 22.3 ± 6.9 hours.

In another study,[17] 8 fasted volunteers received phenytoin 15 mg/kg intravenously over 1 hour followed by charcoal 140 g over 10 hours (40 g at end of the infusion; 20 g at 2, 4, 6, 8, and 10 hours after the infusion). Half of the subjects received sorbitol in their loading dose and with every other dose of activated charcoal. Administration of activated charcoal led to a significant increase ($p = 0.008$) in mean phenytoin clearance from 15.3 ± 3.8 mL/min/1.73m^2 to 20.9 ± 5.2 mL/min/1.73m^2. There was a nonsignificant decrease in half-life from 25.5 ± 9.8 hours to 23.6 ± 15.9 hours after charcoal. The addition of sorbitol to the treatment regimen did not change clearance values.

Piroxicam. In a study with a randomized crossover design and 6 volunteers, Laufen and Leitold[18] studied the use of multiple-dose activated charcoal following the administration of piroxicam 20 mg by either the oral or rectal route. In the oral drug administration phase, activated charcoal 50 g was administered at 10 hours postingestion followed by doses of 20–30 g for a total of 70 g every 24 hours up to 58 hours after piroxicam ingestion. The elimination half-life was reduced significantly ($p < 0.05$) from a mean (±SD) of 40.2 ± 10.0 hours (control group) to 19.6 ± 5.9 hours (charcoal group). The mean apparent total clearance increased significantly ($p < 0.05$) from

3.46 ± 1.33 mL/min to 5.66 ± 1.41 mL/min. In the rectal administration phase, activated charcoal 30 g was administered at 2 hours after drug delivery and 20–30 g was given at varying intervals for a total of 70 g every 24 hours. The elimination half-life was reduced significantly from a mean (±SD) of 40.7 ± 12.6 hours in the control group to 21.6 ± 6.4 hours in the charcoal group. There was also a significant ($p < 0.05$) increase in the mean (±SD) apparent total clearance from 3.65 ± 1.19 mL/min to 6.86 ± 2.23 mL/min.

Quinine. The effect of multiple-dose activated charcoal on quinine elimination was studied following a therapeutic (600 mg) dose of quinine bisulphate to 7 adult fasted volunteers.[19] Activated charcoal 50 g was administered 4 hours after quinine dosing and 3 further doses were given over the next 12 hours. Activated charcoal significantly lowered ($p < 0.001$) the quinine elimination half-life from 8.23 ± (SD) 0.57 to 4.55 ± 0.15 hours and the clearance was significantly increased ($p < 0.001$) from 11.8 ± (SD) 1.23 L/h to 18.4 ± 2.8 L/h.

Sotalol. The mean elimination half-life of sotalol was decreased significantly ($p < 0.01$) from 9.4 ± (SEM) 0.4 hours to 7.6 ± 0.3 hours by the administration of activated charcoal (50 g at 6 hours, then 12.5 g every 6 hours for 8 doses) to 7 fasted adult volunteers who had received sotalol 160 mg orally.[20]

Theophylline. The effect of activated charcoal on theophylline kinetics when a sustained-release preparation was administered orally to 20 children in a dose of 10 mg/kg was studied by Lim *et al*.[81] Five children given activated charcoal 1 g/kg body weight (maximum 60 g) at 6, 9, and 12 hours postdosing had a 20.65% nonsignificant reduction in the AUC compared to controls.

Minton and Henry[82] administered 3 sustained-release theophylline 200 mg tablets to 10 fasted volunteers. Activated charcoal 50 g was given at 6 hours, with 2 further 25 g doses at 10 hours and 14 hours. The AUC of theophylline in the control group was 152.8 ± (SD) 1.44 mg/L/h and in the charcoal group was 65.3 ± 1.33 mg/L/h. No statistical calculations were undertaken.

Goldberg *et al*.[83] demonstrated that the addition of sorbitol to charcoal significantly reduced ($p < 0.01$) the AUC [85.5 ± (SEM) 10.0 mg/h/L] when compared to multiple-dose charcoal alone (113 ± 5.7 mg/h/L) and controls (304.6 ± 18.8 mg/h/L). In this study, charcoal, with or without sorbitol, was administered at 6, 7, 8, 10, and 12 hours after administration of slow release theophylline 1200 mg/70 kg to 9 subjects.

The effect of multiple-dose charcoal on the kinetics of an intravenous dose of aminophylline (6 mg/kg body weight) administered to 5 volunteers was investigated by Berlinger *et al*.[21] Activated charcoal 40 g was given at time zero and 20 g at 2, 4, 6, 9, and 12 hours after completion of the theophylline infusion. Treatment with activated charcoal significantly decreased ($p < 0.05$) the mean elimination half-life from 6.4 ± (SEM) 1.2 hours to 3.3±0.4 hours. The AUC in the charcoal group was 42 ± 4 mg · h/L compared to 78 ± 14 mg · h/L in controls ($p < 0.05$).

Mahutte *et al*.[23] administered an infusion of aminophylline 8 mg/kg to 7 volunteers. Each then received activated charcoal 30 g at time zero and at 2, 4, and 6 hours. A significant reduction ($p < 0.001$) in the mean theophylline elimination half-life from 10.2 ± (SD) 2.1 hours to 4.6 ± 1.3 hours was observed. The total body clearance of theophylline was also increased significantly ($p < 0.001$) by charcoal administration from 35.6 ± (SD) 7.3mL/kg/h to 72.6 ± 17.0 mL/kg/h.

The effect of different regimens of multiple-dose activated charcoal on the elimination of aminophylline 6 mg/kg given by infusion over 1 hour in 6 volunteers was investigated by Park *et al*.[24] A significant reduction ($p < 0.01$) in the mean theophylline elimination half-life from 9.1 ± (SEM) 0.7 hours was achieved either with charcoal 20 g every 2 hours for 6 doses (4.3 ± 0.4 hours) or 10 g every hour for 6 doses (4.3 ± 0.2 hours). Park *et al*.[25] also gave 8 volunteers aminophylline 5–6 mg/kg intravenously over 60 minutes. Immediately on discontinuing the aminophylline infusions, the volunteers received activated charcoal either 5 g or 20 g every 2 hours for 6 doses. The 20 g regimen produced a significant reduction ($p < 0.01$) in the halflife [4.9 ± (SEM) 0.2 hours] compared to the 5 g regimen (6.3 ± 0.5 hours). The AUC was also reduced significantly ($p < 0.01$) from 88.9 ± 8.4 (5 g regimen) mg/L/h to 67.7 ± 3.6 mg/L/h (20 g regimen).

In another study,[26] 6 subjects with cirrhosis were given multiple-dose activated charcoal (40 g at time zero and 20 g at 2, 4, 6, 9, and 12 hours) following an infusion of aminophylline 6 mg/kg over 1 hour. The mean theophylline half-life during treatment was reduced significantly ($p < 0.05$) from 12.7 ± (SEM) 4.0 hours to 4.0 ± 0.7 hours.

Five fasted volunteers received an infusion of aminophylline 8 mg/kg over 1 hour followed by various activated charcoal regimens: 12.5 g every hour for 8 hours; 25 g every 2 hours for 8 hours; 50 g every 4 hours for 8 hours.[22] Each dosage regimen was preceded by activated charcoal 50 g and each subject received a total of 150 g. The mean theophylline elimination half-life was reduced

significantly ($p < 0.05$) for each charcoal regimen compared to controls, but there was no significant difference between the treatment groups. Similarly, the mean AUC for each charcoal regimen was significantly lower ($p < 0.05$) than controls, although there was no significant difference between the charcoal regimens.

Tobramycin. Davis *et al*.[34] administered tobramycin 2.5 mg/kg intravenously over 30 minutes to 6 volunteers. Activated charcoal 50 g was given prior to tobramycin administration and subsequent doses of 15 g were administered at 2, 4, and 6 hours. There was no difference in the mean values for total body clearance of tobramycin compared to control.

Multiple-dose activated charcoal (10 g 2 hours prior to dosing, 10 g at zero time, and 10 g at 2, 6, and 8 hours after dosing) had no effect on the elimination of tobramycin 1.5 mg/kg administered intravenously in 5 volunteers.[35]

Tricyclic Antidepressants. Kärkkäinen and Neuvonen[37] studied the impact of activated charcoal on the elimination of amitriptyline 75 mg administered orally to 6 fasted volunteers. Activated charcoal 50 g was given 6 hours after amitriptyline dosing and further doses (12.5 g) of charcoal were administered at 12, 18, 24, 30, 36, 42, 48, and 54 hours. Charcoal shortened significantly ($p < 0.05$) the elimination half-life of amitriptyline from 27.4 ± (SEM) 4.8 hours (control) to 21.1 ± 3.3 hours (charcoal group). The $AUC_{0-72\ h}$ was also reduced significantly ($p < 0.05$) in the charcoal group.

In a further study, 8 volunteers were given doxepin 50 mg orally and then received activated charcoal 15 g 3 hours later, followed by charcoal 10 g at 6, 9, 12, and 24 hours after dosing.[38] The half-life in the activated charcoal group [16.2 ± (SEM) 2.3 hours] was not significantly different from the control group (17.9 ± 4.3 hours) and the clearance of doxepin in the activated charcoal group [1.23 ± (SEM) 0.31L/h/kg] was not significantly different from the control group (0.93 ± 0.03 L/h/kg).

The effect of multiple-dose activated charcoal on the elimination of imipramine was studied in a randomized crossover trial.[39] Four fasted volunteers received imipramine 12.5 mg/70 kg intravenously over 1 hour followed by either water or 180 g activated charcoal over 24 hours (20 g at 0, 2, 4, 6, 9, 12, 16, 20, and 24 hours after dosing). There was no significant difference ($p > 0.05$) in imipramine half-life in controls [9.0 ± (SEM) 0.8 hours] compared to the charcoal treated group (10.9 ± 1.6 hours) or in clearance values in the control group (992.2 ± 138.3 mL/min/70 kg) and in the charcoal treated group (930.3 ± 101.9 mL/min/70 kg).

Crome *et al*.[40] administered 4 separate doses of activated charcoal 5 g to 6 volunteers 30, 120, 240, and 360 minutes after they had been given nortriptyline 75 mg orally. There was a mean 72% (range 62–78%) reduction ($p < 0.01$) in peak nortriptyline concentrations and a significant reduction (mean 70%; range 58–76%; $p < 0.01$) in $AUC_{0-48\ h}$ compared to control after multiple doses of charcoal. When only a single dose of activated charcoal 5 g was administered 30 minutes after nortriptyline, there was a mean 58% (range 30–81%) reduction in peak plasma nortriptyline concentrations and a mean 55% (range 32–67%) reduction in $AUC_{0-48\ h}$. The difference in peak nortriptyline concentrations and $AUC_{0-48\ h}$ after single- and multiple-dose charcoal therapy was also significant ($p < 0.05$).

Valproic Acid. Following the oral administration of sodium valproate 300 mg to 7 volunteers, multiple-dose activated charcoal 20 g was administered at 4 hours; 10 g was given at 8, 12, 24, and 32 hours.[33] Activated charcoal did not significantly change the half-life of sodium valproate which was 20.0 ± (SD) 6.8 hours in the control group and 22 ± 9.2 hours in the charcoal group. The $AUC_{0-48\ h}$ after activated charcoal was 408.0 ± (SD)114.5 mg/L/h which was not significantly different from control (398.1 ± 108.6 mg/L/h).

Vancomycin. Davis *et al*.[36] investigated the role of multiple-dose activated charcoal after the administration of vancomycin 1 g intravenously to 6 volunteers. Activated charcoal 50 g was administered before the infusion followed by 15 g doses at 2, 4, 6, and 8 hours after the start of the vancomycin infusion. Multiple-dose activated charcoal therapy did not enhance vancomycin clearance.

CLINICAL STUDIES

Clinical studies of multiple-dose activated charcoal consist only of case series and case reports.

Aspirin. Hillman and Prescott[56] described 5 patients with salicylate poisoning whose peak plasma salicylate concentrations were 425–655 mg/L. In 2 cases where the salicylate concentration exceeded 500 mg/L, alkaline diuresis was employed initially. All patients received multiple-dose activated charcoal (75 g, then 50 g every 4 hours) until their symptoms resolved. However, the charcoal preparation administered (Medicoal) contains substantial amounts of sodium bicarbonate and all patients developed an alkaline urine (personal communication) which may have further increased salicylate elimination. In a control group (selection criteria were not stated) of

6 patients with mild salicylate poisoning who were treated with oral fluids alone, the mean elimination half-life was 27 hours, whereas the mean half-life in the treatment group was less than 3.2 hours.

In 7 patients, all of whom had salicylate concentrations greater than 500 mg/L and who received no other therapy, Vale[57] found the elimination half-life to be 9.7 ± (SD) 3.0 hours after each received at least 12.5 g/h activated charcoal. However, no control data were included in this case series.

Conclusion. One animal study and 2 of 4 volunteer studies did not demonstrate increased salicylate clearance with multiple-dose charcoal therapy. Data in poisoned patients are insufficient to recommend the use of charcoal therapy.

Carbamazepine. After multiple-dose activated charcoal (mean total dose 203 ± 58 g), the mean elimination half-life in 15 patients poisoned with carbamazepine was 8.6 ± (SD) 2.4 hours and the mean total body clearance was 113 ± (SD) 44 mL/min,[41] whereas in 2 other series of patients treated only with supportive measures,[84,85] the mean elimination half-life was approximately 19 hours [19.0 ± (SD) 6.9 hours[84] and 18.9 ± (SD) 9.8 hours[85]].

Montoya-Cabrera *et al*.[42] administered multiple-dose activated charcoal (1 g/kg every 4 hours) to 8 patients (mean total dose 386 ± 72 g). The mean (±SD) carbamazepine half-life was 9.5 ± 1.9 hours and the mean (±SD) total body clearance was 105.13 ± 20.4 mL/min/kg.

The role of multiple-dose charcoal in carbamazepine poisoning was questioned by Wason *et al*.[86] who reported on its use in 2 children with acute and 2 (1 with 2 episodes of poisoning) with acute-on-chronic carbamazepine intoxication. The peak carbamazepine concentrations in this study were between 22.4 and 60.0 mg/L. The mean elimination half-life of carbamazepine was 23.3 hours (1 case) without charcoal, 10.17 hours ($p < 0.05$) when activated charcoal 30–50 g was given (2 episodes of poisoning), and 7.21 hours ($p < 0.05$) when more than charcoal 50 g was used (3 episodes of poisoning). The authors reported no benefit from multiple-dose charcoal in terms of time to complete recovery despite the effect on the plasma half-life of the drug. However, this conclusion has been criticized by Vale and Heath[87] who stated that the study was too small to test reliably the hypothesis that there exists a relationship between the dose of activated charcoal and time to recovery.

Conclusion. There is good evidence from animal and volunteer studies and from poisoned patients that the total body clearance of carbamazepine is enhanced significantly by multiple-dose activated charcoal therapy. In terms of total body clearance, multiple-dose charcoal is comparable to charcoal hemoperfusion (Table 1). However, a reduction in morbidity has not yet been demonstrated by its use.

Table 1

Comparison of Elimination Techniques in Carbamazepine Poisoning

Elimination	Half-life (hours)	Clearance (mL/min)
Hemoperfusion	8.6–10.7[90]	80–129[89–91]
Multiple-dose charcoal	8.6 ± 2.4[41]	113 ± 44[41]
Multiple-dose charcoal	9.5 ± 1.9[41]	105.13 ± 20.4[41]

Dapsone. Neuvonen *et al*.[6] described 2 patients with dapsone poisoning. One received activated charcoal 20 g every 6 hours on days 5 and 6 postingestion, with a reduction in the elimination half-life from 88 to 13.5 hours. The second patient received charcoal 20 g every 6 hours only on the third day postoverdose. A reduction in the dapsone elimination half-life from 33 to 11 hours approximately was observed. Workers from the same unit[43] reported a further 3 patients with dapsone poisoning. The initial dapsone concentrations measured between 16–47 hours after ingestion were 28.0, 23.6, and 17.5 mg/L, respectively. Oral activated charcoal 20 g every 6 hours was administered for 1 to 2 days beginning 2 to 4 days postingestion. The mean dapsone elimination half-life was reduced from 77 ± (SEM) 23 hours to 12.7 ± 0.7 hours.

Conclusion. Volunteer studies demonstrate that multiple-dose activated charcoal increases dapsone elimination. Clinical data support this conclusion and the elimination half-life achieved by charcoal is comparable to that (10.4 ± 1.7 hours) during hemodialysis.[43] However, it has not been demonstrated that methemoglobinemia and hemolytic anemia are less likely to result after the use of charcoal therapy.

Digitoxin. Pond *et al*.[62] advocated the use of multiple-dose activated charcoal in digitoxin poisoning, based on their experience of a patient with a peak plasma digitoxin concentration of 264 μg/L who received activated charcoal 50 g initially, then 60 g (with magnesium citrate 250 mL) every 8 hours for 72 hours. Following charcoal, the digitoxin half-life was 18 hours compared to a half-life of 162 hours after discontinuation of charcoal.

Conclusion. Volunteer studies and 1 case report suggest that the clearance of digitoxin may be increased by multiple-dose activated charcoal, though clinical benefit has yet to be demonstrated. However, in severe cases of poisoning, digoxin-specific antibody fragments should be considered.

Digoxin. Boldy *et al*.[58] described a 69-year-old man who had ingested a digoxin overdose and had a plasma digoxin concentration of 8.3 μg/L, 14.5 hours postingestion. He received activated charcoal 100 g over 1 hour, then 50 g every 4 hours for a further 7 doses. The plasma digoxin concentration fell to 1.0 μg/L over the ensuing 48 hours with a terminal elimination half-life of 14 hours.

Lake *et al*.[59] reported a 71-year-old woman with chronic renal failure and digoxin toxicity (peak plasma concentration 9 μg/L) who was treated with activated charcoal 50 g followed by 25 g every 6 hours for 8 doses. The digoxin elimination half-lives calculated before, during, and after charcoal therapy were 7.3, 1.4, and 6.3 days, respectively.

Critchley and Critchley [60] described a 66-year-old male with an 8-year history of chronic renal failure who was suffering from digoxin toxicity (severe bradycardia and hypotension). The patient's serum digoxin concentration failed to decrease over 4 days despite the use of daily hemodialysis. On day 4, multiple-dose activated charcoal therapy was instituted (50 g every 6 hours for 48 hours). The serum digoxin concentration decreased from 2.1 μg/L to 0.8 μg/L within 48 hours. A second course of activated charcoal (50 g every 6 hours for 72 hours) was instituted from admission day 9 to 12, resulting in a decrease in the digoxin concentration from 0.8 μg/L to 0.4 μg/L. During each course of activated charcoal therapy, there was a precipitous reduction in the serum half-life of digoxin, but precise half-lives were not calculated.

Multiple-dose activated charcoal (dose not stated) increased the mean digoxin clearance in 23 patients to 98 ± (SD) 34 mL/min (mean clearance in 16 nontreated patients 55 ± 17 mL/min) and decreased the digoxin elimination half-life from 68 ± (SD) 19 hours to 36 ± 14 hours (control group); all patients had plasma digoxin concentrations >2.5 μg/L.[61]

Conclusion. The elimination half-life of digoxin was decreased by the use of multiple-dose activated charcoal in animal and volunteer studies, in 2 case reports and 1 case series. However, in severe cases of poisoning, digoxin-specific antibody fragments should be considered.

Meprobamate. Hassan[65] described a further 2 patients with meprobamate poisoning whose peak plasma concentrations were 320 mg/L and 240 mg/L. Each received oral activated charcoal 50 g every 4 to 6 hours for 5 doses after an initial loading dose (75 g in 1 patient). The elimination half-lives for meprobamate were 4.4 hours and 4.5 hours, respectively.

Three patients with meprobamate poisoning were treated with multiple-dose activated charcoal.[66] Peak meprobamate concentrations were 221 mg/L, 91 mg/L, and 80.5 mg/L, respectively and all patients initially required mechanical ventilation. With charcoal therapy, the elimination half-lives for meprobamate were 4.0, 4.5, and 5.0 hours, respectively.

Conclusion. Reports of meprobamate poisoning managed without multiple-dose charcoal suggest an elimination half-life of about 13 hours[92] and thus charcoal therapy may be effective in increasing drug elimination though there are no volunteer studies to confirm this.

Methotrexate. Serum methotrexate concentrations were estimated after a 6-hour infusion of 1 g/m^2 methotrexate had been administered to 7 patients.[67] Each received activated charcoal 25 g at 12, 18, 24, 36, and 48 hours after the infusion. The elimination half-life in the charcoal treated group was reduced, but not significantly, from 8.46 ± (SEM) 0.47 hours (controls) to 7.6 ± 0.44 hours (charcoal group).

Conclusion. This single study does not support the clinical use of multiple-dose activated charcoal after high-dose methotrexate therapy.

Phenobarbital (Phenobarbitone). Goldberg and Berlinger[44] gave multiple-dose activated charcoal to 2 patients poisoned with phenobarbital. The first patient (serum phenobarbital concentration 141 mg/L) received activated charcoal 40 g (with sodium sulfate 20 g) on admission and activated charcoal 40 g (with magnesium citrate 60 mL) every 4 hours for 5 additional doses. The second patient (serum concentration 107 mg/L) was given activated charcoal 30 g (and sodium sulfate 30 g) 6 hours after admission and this dose was continued every 6 hours for a total of 6 doses. The phenobarbital elimination half-lives in these 2 patients were approximately 24 hours.

A randomized study of 10 comatose patients who required endotracheal intubation and mechanical ventilation was reported by Pond *et al*.[45] The control group (n = 5) who received only a single dose of activated charcoal (mean plasma phenobarbital concentration 121 ± 31 mg/L) and the treatment group (n = 5) who received multiple doses of activated charcoal (mean plasma phenobarbital concentration 132 ± 36 mg/L) both received activated charcoal 50 g with magnesium citrate 250 mL on presentation and, in addition, patients in the treatment group were given activated charcoal 17 g together with

sorbitol 70 mL (70%) every 4 hours until they had recovered sufficiently to be extubated. Although the mean elimination half-life of phenobarbital was shortened (36 ± (SD) 13 hours) significantly ($p < 0.01$) in the multiple-dose charcoal treatment group when compared to the single-dose charcoal group (93 ± 52 hours), the length of time that the patients in each group required mechanical ventilation did not differ significantly and nor did the time spent in hospital. This trial has been criticized as being too small and having unevenly matched groups.[93,94]

In another series,[46] charcoal, in larger doses and given without cathartic, not only greatly enhanced the elimination of phenobarbital, but also decreased the time to recovery. Six patients with moderate to severe phenobarbital intoxication (mean peak plasma phenobarbital concentration 139.2 ± 76.8 mg/L) were treated with repeated oral doses of activated charcoal 50 g (in 3 cases the charcoal employed contained sodium bicarbonate) following an initial dose of 50 to 150 g (total dose 225–500 g). During and for up to 12 hours after treatment with activated charcoal, the mean phenobarbital half-life was 11.7 ± 3.5 hours. The mean total body clearance of the drug during and up to 12 hours after administration of charcoal was 84 ± 34 mL/min. It is possible that in the 3 patients receiving sodium bicarbonate, renal clearance of phenobarbital may have been enhanced. It should be noted that only one third of the patients in this series were receiving long-term anticonvulsant therapy, in contrast to 100% of patients in the study reported by Pond *et al*.[45]

The administration of 6 doses of activated charcoal (0.7 g/kg) to a severely brain-damaged neonate (weight 2.6 kg), treated with intravenous phenobarbital (50 mg/kg), decreased the serum phenobarbital half-life from a calculated 250 hours to 22 hours, enabling earlier initiation of brain stem testing.[47]

Conclusion. There is good evidence from animal and volunteer studies and from poisoned patients that the total body clearance of phenobarbital is enhanced significantly by multiple-dose activated charcoal therapy. In terms of total body clearance, multiple dose charcoal is comparable to other elimination techniques such as hemodialysis and hemoperfusion (Table 2).

Table 2

Comparison of Elimination Techniques in Phenobarbital Poisoning

Elimination	Clearance (mL/min)
Intrinsic clearance	4[95]
Alkaline diuresis	7[96]
Hemodialysis	49[97]
Hemoperfusion	77[96,98]
Multiple-dose charcoal	84[46]*

* Estimated.

Phenytoin. A 21-year-old woman presented 9 hours after allegedly ingesting phenytoin 20 g and was treated with 3 doses (amount not stated) of activated charcoal every 2 hours (time after overdose not stated). The phenytoin concentration fell from 41 mg/L on admission to 11 mg/L on day 5 postoverdose.[68]

Howard *et al*.[69] reported the clinical course of a 36-year-old, hepatitis B–positive, chronic alcohol abuser receiving both phenobarbital and phenytoin long-term for epilepsy. Twenty-four hours before admission his plasma phenytoin concentration was 34 mg/L and on admission 47 mg/L, at which time features of phenytoin toxicity were present. He received activated charcoal 50 g with sorbitol 96 g every 6 hours for 4 doses. The phenytoin concentration decreased to 20 mg/L approximately 44 hours after admission. Since it is likely that this patient had taken an acute overdose of phenytoin and had induced hepatic enzymes, the benefit of multiple-dose activated charcoal is difficult to determine.

Ros and Black[70] described a 17-year-old epileptic whose serum phenytoin concentration at admission was 56 mg/L, rising to 69 mg/L after 24 hours. He was then treated with 9 doses of activated charcoal 30 g every 4 hours. Thirty-eight hours after the first dose of charcoal, the serum phenytoin concentration had fallen to 22 mg/L. When charcoal was discontinued, the serum phenytoin concentration increased to 33 mg/L, then slowly declined.

Weichbrodt and Elliott[71] reported a 38-year-old woman on long-term phenytoin therapy who was treated with multiple-dose activated charcoal after an overdose of phenytoin 10–15 g. She received an initial dose of activated charcoal 30 g at 7 hours postoverdose, followed by 30 g every 6 hours for 4.5 days commencing some 30 hours after overdose (magnesium citrate 180 mL was co-administered with each dose). Her peak serum phenytoin concentration (52 mg/L) was reached within 42.5 hours and the phenytoin concentration fell to within the therapeutic range 6 days postoverdose.

A further case of chronic phenytoin intoxication in a patient with severe liver disease was reported by Weidle *et al*.[72] Seven days after commencing phenytoin 300 mg twice daily, the patient became agitated and incoherent and the serum phenytoin concentration was found to be

44.4 mg/L. Phenytoin was discontinued and 2 days later (phenytoin concentration 45.2 mg/L) she was commenced on a multiple-dose charcoal regimen of 30 g every 4 hours. After 10 doses of charcoal, the serum phenytoin concentration was 11.4 mg/L. The authors estimated that the clearance had been increased by approximately 1.65 L/h/1.78 m^2.

Conclusion. Although there is some evidence from animal and volunteer studies that multiple-dose activated charcoal may enhance phenytoin elimination, the 5 anecdotal case reports published to date do not confirm that this therapeutic approach is of clinical benefit.

Quinine. In 5 symptomatic patients with acute quinine poisoning, the mean elimination half-life was 8.1 ± (SD) 1.1 hours after each had been administered activated charcoal 50 g every 4 hours.[48] This should be compared to a half-life of approximately 26 hours in poisoned patients treated supportively.[99]

Conclusion. A volunteer study has demonstrated that quinine elimination is enhanced significantly by multiple-dose activated charcoal and a single clinical study has confirmed this observation, even though the relatively large volume of distribution (>1–2.7 L/kg) and high protein binding (70–90%) do not favor the use of charcoal therapy. Further studies are required to demonstrate that the serious sequelae encountered in quinine poisoning are reduced or even abolished by charcoal therapy.

Theophylline Poisoning. Mahutte *et al*.[23] reported a 72-year-old man with theophylline poisoning (admission concentration 31 mg/L) in whom 4 doses of activated charcoal 30 g every 2 hours reduced the pretreatment half-life from 34.4 to 5.7 hours. Workers from the same unit subsequently described 4 further patients [mean ± (SD) pretreatment theophylline concentrations were 37.1 ± 11.25 mg/L] in whom multiple-dose charcoal reduced the mean serum theophylline half-life from 23.30 ± (SD) 7.95 hours to 8.0 ± 3.95 hours.[55]

Five patients with moderate theophylline poisoning who were treated with multiple-dose charcoal were reported by Radomski *et al*.[26] The mean serum theophylline half-life (±SEM) was 4.9 ± 0.8 hours with peak serum theophylline concentrations ranging from 32–59 mg/L.

Amitai *et al*.[49] reported 2 patients (a 34-year-old woman and a 5-month-old infant) with theophylline poisoning (peak plasma concentrations 100 mg/L and 97 mg/L, respectively). With activated charcoal 15 g hourly for 9 doses commencing 14 hours after overdose, the adult patient's theophylline elimination half-life fell to 3.7 hours. The infant received 3 doses of activated charcoal: 10 g at 4.5 hours, 5 g at 8 hours, and 2.5 g at 11 hours postoverdose. The initial elimination half-life of 19 hours decreased to 2.4 hours after charcoal.

Following a medical error,[50] a patient with a peak theophylline concentration of 42.5 mg/L was treated with multiple-dose activated charcoal 15 g every 2 hours for 4 doses and the elimination half-life was reduced from 7.5 to 2.2 hours.

A 23-year-old woman attempted suicide by ingesting theophylline and terbutaline tablets.[51] The peak (on admission) serum theophylline concentration was 111.4 mg/L. Treatment with multiple-dose activated charcoal 50 g every 6 hours led to a reduction in the theophylline half-life from 17.2 to 5.9 hours.

Two adolescents with serum theophylline concentrations greater than 100 mg/L were treated with a continuous nasogastric infusion of activated charcoal at a maximum rate of 50 g/h.[52] During the first 20 hours of charcoal therapy, the elimination half-life of theophylline was estimated as 7.7 and 13.5 hours, respectively, decreasing subsequently to 2.6 and 3.2 hours.

Sessler *et al*.[53] reported 14 cases of theophylline poisoning, 10 of whom were treated with activated charcoal. Although several patients vomited charcoal, the mean theophylline half-life during charcoal therapy was 5.6 ± (SD) 2.5 hours.

A further 5 cases, including one reported previously by Amitai *et al*.[49] of theophylline poisoning due to medical error in infants under 7 months old, were reported by Shannon *et al*.[54] Multiple-dose activated charcoal resulted in an elimination half-life of 8.3 ± (SD) 4.7 hours (n = 4).

Conclusion. Patients poisoned severely with theophylline are invariably vomiting repeatedly which makes administration of charcoal problematic, even via a nasogastric tube. In these circumstances the use of an antiemetic intravenously should be considered. Studies in animals and volunteers confirm that the elimination of theophylline is enhanced by multiple-dose activated charcoal. Case reports also suggest that theophylline elimination is increased by this means although further studies are required to demonstrate that morbidity is reduced by multiple-dose charcoal therapy.

Tricyclic Antidepressants. Swartz and Sherman[73] administered activated charcoal to 3 patients poisoned with amitriptyline. The first patient received 2 doses (50 g at 2 hours and 25 g at 10 hours postoverdose) of activated charcoal, the second patient received 3 doses (50 g at 2 hours, 25 g at 6 hours, and 25 g at 23 hours postoverdose), and the third patient received 4 doses (40 g at 1 hour, 20 g at 4 hours, 20 g at 9 hours, and 20 g at 21 hours postoverdose) of activated charcoal. Although the authors concluded that charcoal ''greatly accelerated tricyclic elimination,'' this cannot be supported from the data.

Three patients poisoned with dothiepin received activated charcoal 100–200 g following overdose.[74] The mean elimination half-life was 12.1 ± (SD) 1.3 hours, which is not substantially different from cases treated supportively in the same series.

Conclusion. A variable effect on the elimination half-life of amitriptyline, doxepin, and imipramine has been reported in volunteer studies. However, it would not be expected from the very large volume of distribution of tricyclic antidepressants that their elimination would be enhanced by activated charcoal.

Valproic Acid. A 26-month-old infant ingested a minimum of 4.5 g enteric-coated valproic acid. On arrival at hospital, activated charcoal 20 g was administered (no detectable valproic acid in the serum) and following a marked clinical deterioration (serum valproic acid 315 mg/L), gastric infusion of 3 g/h activated charcoal was given from 9 hours to 25 hours postoverdose.[75] The elimination half-life was 4.8 hours, which is shorter than the 23 hours reported by Dupuis *et al*.[100]

Conclusion. The elimination of sodium valproate was not enhanced in animal and volunteer studies by the use of multiple-dose charcoal therapy. It is possible that at higher plasma drug concentrations, when more free drug is likely to be present, such therapy could have greater benefit. Further studies are needed to confirm this.

Vancomycin. A 17-day-old neonate was administered vancomycin 500 mg intravenously. Multiple-dose activated charcoal 1 g/kg was administered 5 hours later and continued every 4 hours for 12 doses.[64] The half-life of vancomycin was calculated to be 9.4 hours.

A 47-day-old premature neonate received an overdose of vancomycin as a result of medical error. Exchange transfusion did not change the measured serum vancomycin concentration. Multiple doses of activated charcoal 1 g/kg were administered through a nasogastric tube every 4 hours (9 doses in all) beginning 5 hours after exchange transfusion. The calculated half-life prior to and after charcoal therapy was 35 hours and 12 hours, respectively. During therapy the serum vancomycin concentration fell from 230 mg/L to 42 mg/L.[63]

Conclusion. The elimination of vancomycin was not increased by multiple-dose activated charcoal in a volunteer study. The apparent greater benefit of this treatment in 2 case reports is suggestive of benefit but further studies are required to confirm efficacy.

DOSAGE REGIMEN

If multiple-dose activated charcoal is considered appropriate, it is essential that the staff undertaking the procedure are experienced in its use both to reassure the conscious patient and to reduce the risk of complications in the obtunded patient.

A patient should be told that large and repeated doses of activated charcoal need to be given and that its administration may lead to a faster recovery. If appropriate, the patient should be informed that the treatment is to be given via a nasogastric tube. Such an approach is mandatory if the patient is unconscious but may also be necessary if the individual is nauseated or vomiting.

If a patient has ingested a drug in overdose which induces nausea and vomiting, the administration of activated charcoal, particularly if it contains sorbitol, may produce emesis. In these circumstances it is appropriate to administer an antiemetic intravenously to ensure compliance. Alternatively, smaller, more frequent doses of charcoal may be used but are not always retained.

The dose of administered charcoal is probably of greater importance than the surface area of the charcoal.[101] In a study involving 6 volunteers, activated charcoal 20 g, given every 2 hours, produced a significantly greater reduction in the half-life of theophylline than 5 g every 2 hours.[24] In addition, administering the same total dose of activated charcoal (120 g over 12 hours) in hourly doses rather than less frequently resulted in a further reduction in half-life. Ilkhanipour *et al*.[22] have also confirmed that activated charcoal 12.5 g every hour (total dose 150 g over 12 hours) produced the greatest reduction in theophylline elimination half-life. Moreover, the more frequent administration of smaller doses of activated charcoal tends to prevent regurgitation which commonly occurs when large doses are given. There is some evidence that a continuous gastric infusion of charcoal, at least after a large initial dose (50–100 g), may offer advantages.[52]

Clinical experience suggests that, after an initial dose of 50–100 g given to an adult, charcoal may be administered hourly, every 2 hours, or every 4 hours at a dose equivalent to 12.5 g/h. In children, lower doses (10–25 g) of charcoal may be employed because smaller overdoses have usually been ingested and the capacity of the gut lumen is smaller.

CO-ADMINISTRATION OF A CATHARTIC

The role of cathartics, such as sorbitol, mannitol and sodium, and magnesium sulfate, remains controversial. They are often given at the same time as activated charcoal in order to increase palatability. Sorbitol sweetens the mixture but palatability is not relevant if administra-

tion is via a nasogastric tube. Some studies (but not others) suggest that the co-administration of a cathartic may not only reduce drug adsorption to charcoal but, paradoxically, increase absorption by increasing the volume of intestinal fluid.[102] Furthermore, mannitol and sorbitol delay gastric emptying in man,[103] thereby reducing the amount of charcoal available to adsorb the drug in the small bowel. More recent evidence, however, indicates that in man the co-administration of a cathartic to charcoal may further hasten the elimination of phenobarbital[14] and of a slow-release theophylline preparation,[83] although the combined use of sorbitol and charcoal was not without adverse effects. Two of the 9 volunteers in the latter study developed liquid stools, severe abdominal cramps, nausea, sweating, and hypotension. However, Al-Shareef *et al*.[104] did not demonstrate an additional benefit from the use of a sorbitol-charcoal formulation in the management of theophylline poisoning. Cathartics theoretically decrease the risk of constipation and hence small bowel obstruction if very large doses of activated charcoal are administered.

The need for a cathartic as part of a multiple-dose activated charcoal regimen remains unproven and many clinical toxicologists have not found it necessary to employ cathartics in clinical practice. While the use of sorbitol produces a more rapid onset of catharsis without the development of hypermagnesemia associated with the use of magnesium containing cathartics, it too has well recognized complications. It is probable that the increased morbidity from its use will outweigh any potential benefit (see Position Statement on Cathartics[105]) and therefore the concurrent administration of a cathartic is not recommended. In particular, cathartics should not be administered to young children because of the propensity of laxatives to cause fluid and electrolyte imbalance.

COMPLICATIONS OF USE

The administration of multiple-dose activated charcoal rarely produces clinically-important side-effects. Black stools and mild transient constipation are well recognized but constipation is not usually severe enough to require treatment, even if a cathartic has not been co-administered.

Gastrointestinal Complications

An adult patient treated for carbamazepine poisoning with activated charcoal 240 g and magnesium citrate 600 mL developed an ileus which resolved with the administration of additional doses of magnesium citrate.[106] A further case of small bowel obstruction has been reported in a patient poisoned with amitriptyline who required a laparotomy 5 days after admission to remove a charcoal bezoar in the distal ileum; activated charcoal 30–60 g had been given every 4 to 6 hours for 5 days.[107]

Atkinson *et al*.[108] have described a 24-year-old patient intoxicated with barbiturates and benzodiazepines who required a limited right hemicolectomy after he developed small bowel obstruction due to a large bolus of inspissated charcoal in the caecum. A total of 125 g of activated charcoal was administered over 18 hours.

A rectal ulcer with massive hemorrhage followed the administration of activated charcoal 50 g with magnesium sulfate 50 g in a 1000 mL slurry every 4 to 6 hours for 50 hours to a patient with organophosphorus insecticide poisoning.[109] Bloody stools did not occur until 10 days after she had ingested fenitrothion and passed hard charcoal masses.

Goulbourne and Cisek[110] have reported the development of gastrointestinal obstruction 5 days after a patient poisoned with theophylline was given activated charcoal 350 g. The patient underwent laparotomy with lysis of low-grade adhesions at the ileo-caecal region, for which an ileotransverse colostomy was performed. On opening the bowel, several charcoal clumps were removed measuring $4.5 \times 5 \times 3$ cm.

An obstructing charcoal mass (120 g) was found at the site of an intestinal perforation in a 39-year-old female who was receiving maintenance methadone and who had ingested a modest overdose of amitriptyline.[111] Apart from lethargy, she was asymptomatic but was prescribed activated charcoal 50 g every 4 hours; she declined more than 100 g. Four days later after 2 enemas, perforation occurred.

Respiratory Complications

In some reports it is unclear whether the respiratory complications described were due to the well recognized consequences of aspiration of gastric contents into the lung or the aspiration of activated charcoal specifically. In one instance the presence of povidone in the charcoal formulation was thought to be the major factor.[112]

Severe airway obstruction has been reported in one infant given charcoal after vomiting was induced by syrup of ipecac.[113] Accidental administration of activated charcoal into the lung produced an adult respiratory distress syndrome but the patient recovered and was discharged home 14 days later.[114] Even if recovery results, cerebral anoxic damage may have occurred.[115] Bronchiolitis obliterans has followed aspiration of activated charcoal with fatal consequences.[116]

Six cases of fatal pulmonary aspiration of charcoal have been reported,[112,117–119] but in 1 case[112] this was probably due to the povidone in the formulation rather than to activated charcoal itself.

Fluid, Electrolyte, and Acid-Base Abnormalities

The co-administration of cathartics may produce hypernatremia,[120–122] hypokalemia, hypermagnesemia,[123–124] and metabolic acidosis, particularly in infants.

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