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POSITION PAPER

Position Paper: Single-Dose Activated Charcoal[#]

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

Single-dose activated charcoal therapy involves the oral administration or instillation by nasogastric tube of an aqueous preparation of activated charcoal after the ingestion of a poison. Volunteer studies demonstrate that the effectiveness of activated charcoal decreases with time. Data using at least 50 g of activated charcoal, showed a mean reduction in absorption of 47.3%, 40.07%, 16.5% and 21.13%, when activated charcoal was administered at 30 minutes, 60 minutes, 120 minutes and 180 minutes, respectively, after dosing. There are no satisfactorily designed clinical studies assessing benefit from single-dose activated charcoal to guide the use of this therapy.

Single-dose activated charcoal should not be administered routinely in the management of poisoned patients. Based on volunteer studies, the administration of activated charcoal may be considered if a patient has ingested a potentially toxic amount of a poison (which is known to be adsorbed to charcoal) up to one hour previously. Although volunteer studies demonstrate that the reduction of drug absorption decreases to values of questionable clinical importance when charcoal is administered at times greater than one hour, the potential for benefit after one hour cannot be excluded. There is no evidence that the administration of activated charcoal improves clinical outcome. Unless a patient has an intact or protected airway, the administration of charcoal is contraindicated. A review of the literature since the preparation of the 1997 Single-dose Activated Charcoal Position Statement revealed no new evidence that would require a revision of the conclusions of the Statement.

Keywords Activated charcoal; Charcoal; Poisoning

SUMMARY STATEMENT

Introduction

Overall, the mortality from acute poisoning is less than one percent. The challenge for clinicians managing poisoned patients is to identify promptly those who are most at risk of developing serious complications and who might potentially benefit, therefore, from gastrointestinal decontamination.

Single-dose activated charcoal therapy involves the oral administration or instillation by nasogastric tube of an aqueous preparation of activated charcoal after the ingestion of a poison.

Rationale

Activated charcoal comes in direct contact with, and adsorbs poisons in the gastrointestinal tract, decreasing the extent of absorption of the poison, thereby reducing or preventing systemic toxicity.

In Vitro Studies

Scores of compounds, including many drugs, have been shown to be adsorbed to activated charcoal to varying degrees (1).

Animal Studies

The administration of activated charcoal in animal studies has produced variable reduction in absorption (1).

Volunteer Studies

The results of 122 comparisons with 46 drugs indicate considerable variation in the absolute amount of charcoal used (0.5–100 g) and the time of administration (up to 360 minutes after ingestion); 84 comparisons took place at ≤ 5 minutes. In these studies when activated charcoal was administered at 30 minutes, there was a mean reduction in absorption of 51.70% (n=7); at 60 minutes the mean reduction was 38.14% (n=16); at 120 minutes the mean reduction was 34.54 % (n=8); at 180 minutes the mean result was 21.13% (n=3); at 240 minutes the mean reduction was 29.33% (n=3) and at 360 minutes the reduction was 14% (n=1).

The data from 48 comparisons involving 26 drugs using at least 50 g of activated charcoal showed a mean reduction in absorption of 47.3% (n=3) when activated charcoal was administered at 30 minutes after dosing; the mean reduction at 60 minutes was 40.07% (n=12); at 120 minutes was 16.50% (n=3); at 180 minutes was 21.13% (n=3); at 240 minutes was 32.50% (n=2); 25 comparisons were made at ≤ 5 minutes.

[#]This Position Statement was prepared initially by PA Chyka and D Seger in 1997 and revised by EP Krenzelok and JA Vale in 2004.

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These volunteer studies demonstrated that the reduction of drug absorption decreases to values of questionable clinical importance when charcoal is administered at times greater than one hour after the ingestion of a poison. However, these values do not take account of the influence of food in the stomach and the presence of a poison that may delay gastric emptying.

Clinical Studies

There are no satisfactorily designed clinical studies assessing benefit from single-dose activated charcoal.

One study (2) of symptomatic patients who received activated charcoal and some form of gastric evacuation (gastric lavage, ipecac, gastric aspiration) showed that patients receiving gastric aspiration and activated charcoal were less likely to be admitted to an intensive care unit.

Indications

Based on volunteer studies, activated charcoal is more likely to produce benefit if administered within one hour of poison ingestion.

The administration of activated charcoal may be considered if a patient has ingested a potentially toxic amount of a poison up to one hour following ingestion.

Although volunteer studies demonstrate that the reduction of drug absorption decreases to values of questionable clinical importance when charcoal is administered at times greater than one hour, the potential for benefit after one hour cannot be excluded.

Dosage Regimen

The optimal dose of activated charcoal for poisoned patients is unknown, though available data imply a dose-response relationship that favors larger doses.

Data derived from animal and human volunteer studies have little relevance to the clinical situation because these experimental studies were performed in fasting animals and human subjects who ingested a known quantity of drug.

The *United States Pharmacopeia* (USP DI, 2003) recommends the following oral dosage regimen.

Children up to one year of age: 10–25 g or 0.5–1.0 g/kg
Children 1 to 12 years of age: 25–50 g or 0.5–1.0 g/kg
Adolescents and adults: 25 to 100 g

Contraindications

Activated charcoal is contraindicated if the patient has an unprotected airway, such as in a patient with a depressed state of consciousness without endotracheal intubation. Activated charcoal is also contraindicated if its use increases the risk and severity of aspiration (e.g., a hydrocarbon with a high aspiration potential). Patients who are at risk of hemorrhage or gastrointestinal perforation due to pathology, recent surgery or medical conditions could be further compromised by single-dose activated charcoal. The presence of activated charcoal in the gastrointestinal tract may obscure endoscopic visualization, but a corrosive is not an absolute contraindication when charcoal is used for co-ingested agents that are systemic toxins.

Complications

Considering the widespread use of single-dose activated charcoal, there are relatively few reports of activated charcoal-related adverse effects in the literature. The majority of adverse events are not related to the appropriate use of activated charcoal, but are a complication of aspiration or the direct administration of charcoal into the lung. Aspiration of charcoal containing povidone has led occasionally to major respiratory problems (3).

There are no reports of gastrointestinal obstruction, constipation or hemorrhagic rectal ulceration associated with single-dose activated charcoal therapy. Following the administration of aqueous activated charcoal, emesis occurs infrequently. However, the incidence of emesis appears to be greater when activated charcoal is administered with sorbitol (4,5).

Corneal abrasions may occur upon direct ocular contact (6).

SUPPORTING DOCUMENTATION

Introduction

Single-dose activated charcoal has been used extensively for the last 100 years for the treatment of poison ingestions and continues to be the most common form of gastrointestinal decontamination for the poisoned patient (1,7). However, the use of activated charcoal has declined steadily from a high of 7.7% in 1995 to 5.9% in 2003 as reported by the American Association of Poison Control Centers Toxic Exposure Surveillance System (7).

Controlled pyrolysis of coconut shells, peat, lignite (coal), wood, or petroleum produces charcoal, which is then activated by heating it in steam, air, or carbon dioxide at 600–900°C. The charcoal is washed with inorganic acids and dried. Activation creates a highly developed internal pore structure and small particle size. These factors determine the extent of adsorption at equilibrium (1). The adsorptive surface of activated charcoal contains several carbon moieties (e.g. carbonyl, hydroxyl) that adsorb a poison with varying affinity (8). *In vitro* adsorption to activated charcoal in aqueous solutions is a nonspecific process that reaches equilibrium in less than 30 minutes (9). Desorption of poison may occur because substance adsorption to activated charcoal is a reversible process (1) but the extent and clinical impact of this phenomenon have not been determined.

Medicinal charcoal must meet BP, USP or similar standards for adsorption, microbial contaminants and purity. It typically has a surface area of 950 to 2,000 m^2/g. A super-activated charcoal with a surface area of 3150 m^2/g is not currently available for therapeutic use and will not be considered in this

Position Paper. Some aqueous formulations of activated charcoal contain preservatives, sorbitol, sodium bicarbonate or povidone, which may cause complications (3) or potentially alter efficacy (1,10–13). Tablets and capsules containing activated charcoal are unsuitable for the treatment of poisonings because the rate and extent of adsorption in *in vitro* (9,14) and human volunteer (9,15) studies are inferior to comparable amounts of powdered charcoal dispersed in water.

Rationale

Activated charcoal adsorbs the poison in the gastrointestinal tract, minimizing the extent of systemic absorption of the poison, thereby reducing or preventing systemic toxicity. In order for single-dose activated charcoal to be effective in reducing poison absorption, it must come in direct contact with the poison. Furthermore, when indicated, activated charcoal should be used as soon as possible after the ingestion of a poison, as a delay in charcoal administration reduces its effectiveness.

In Vitro Studies

Methods to test the *in vitro* adsorption of substances to activated charcoal have been proposed since 1900, but there is no international standard for medicinal charcoal. Different pharmacopoeia (e.g., BP, USP) specify the use of different compounds, (e.g. phenol, antipyrine, iodine, methylene blue, or strychnine sulfate) to determine acceptable adsorptive properties of activated charcoal; these test compounds may not be representative of all important toxic compounds. Alternative techniques that are more representative of drug adsorption have been proposed (11). Adsorption to activated charcoal may be assessed *in vitro* either by calculating adsorption isotherms or by screening tests. Adsorption isotherms estimate the adsorptive capacity (i.e., the maximum amount of drug adsorbed by one gram of charcoal) for the substance at an equilibrium of adsorption and desorption by measuring the ratio of free to total drug over a range of charcoal to drug ratios. Both the total drug concentration and temperature are held constant. Screening tests involve a fixed concentration of a substance and activated charcoal in an aqueous system.

Using these experimental approaches, many compounds have been shown to be adsorbed to activated charcoal to some degree (1,12,16), while others are adsorbed very poorly. The chief value of *in vitro* studies is to identify substances that are not adsorbed by activated charcoal.

In vitro experiments have demonstrated several factors that can influence adsorption to activated charcoal such as temperature, pore size of charcoal, particle size of charcoal, surface area of charcoal, solubility of the poison, ionization state of the poison, pH, presence of inorganic salts, and gastric contents (1,17,18). Although several of these factors may be considered in product formulation (10), most of these factors cannot be controlled during the care of a poisoned patient. No consistent relationship between the maximum adsorptive capacity of activated charcoal and the physico-chemical characteristics (e.g. pKa, molecular weight) of drugs has been elucidated to date (19).

Impact of Activated Charcoal Dose and Particle Size on Adsorption

The optimal dose of activated charcoal for poisoned patients is unknown, though available data derived from experimental studies imply a dose-response relationship that favors larger doses (20–22). Chin et al. (22) used a rat model to investigate the optimal antidotal dose of activated charcoal. The study (Table 1) quantified the ability of activated charcoal to adsorb pentobarbital, chloroquine and isoniazid with increasing charcoal to drug ratios of 1:1, 2:1, 4:1 and 8:1. With an increasing charcoal:drug ratio, there was a reduction in plasma drug concentrations

Nakamura et al.(23) studied the *in vitro* effect of activated charcoal particle size on the adsorptive affinity for theophylline. Activated charcoal of five different particle sizes from 10–100 mesh was incubated with theophylline. All experiments were conducted in solutions of either water or physiologic saline. The solutions were not modified to simulate a gastric environment. The adsorption isotherms were applied to the Freundlich equation and expressed as the amount of theophylline (mg) adsorbed per gram of charcoal. Descriptive statistics were used, making it impossible to evaluate the influence of mesh size on the adsorptive capability of each charcoal. There were large differences between the amount of theophylline adsorbed when comparing water to physiological saline. The saline solutions appeared to enhance adsorptive capacity, especially at lower theophylline concentrations. Smaller particle size was associated with more rapid adsorption of the theophylline.

TABLE 1
Adsorption of drugs to charcoal at different charcoal to drug ratios in a rat model [after Chin et al. (22)]

Drug	Charcoal: drug ratio	% Reduction (±SD) in drug concentrations
Phenobarbital	1:1	7.0±2.6
	2:1	38±3.5
	4:1	62±3.7
	8:1	89±2.2
Chloroquine	1:1	20±8.2
	2:1	30±6.5
	4:1	70±1.5
	8:1	96±1.4
Isoniazid	1:1	1.2±1.2
	2:1	7.2±2.6
	4:1	35±5.3
	8:1	80±1.6

Heogberg et al. (24) investigated the *in vitro* adsorptive affinity of two different activated charcoal products for paracetamol. and the affect of ethanol on the adsorptive properties of activated charcoal. Paracetamol was incubated with activated charcoal in activated charcoal:paracetamol ratios of 1:1, 2:1, 3:1, 5:1, 10:1 in simulated gastric and intestinal environments of pH 1.2 and 7.2, respectively. The Langmuir adsorption isotherms were used to determine the adsorption of paracetamol to activated charcoal. The Langmuir plots demonstrated the high affinity of both charcoals for paracetamol at pH 1.2 and 7.2.

Impact of Ethanol on Drug Adsorption to Charcoal

Heogberg et al. (24) investigated the effect of ethanol on the adsorptive properties of activated charcoal. Ethanol 10% v/v was incubated with activated charcoal 250 mg and with the activated charcoal and paracetamol mixtures(activated charcoal: paracetamol ratios of 1:1, 2:1, 3:1, 5:1, 10:1). Ethanol was not adsorbed by activated charcoal significantly. However, ethanol caused a statistically significant reduction in the maximal adsorptive capacity of charcoal of 11.0–11.3% with Norit Supra A and a 20.4–25.3% reduction with Carbomix. The authors concluded that ethanol changed the polarity of paracetamol and decreased its binding to charcoal and that Norit Supra may be clinically superior to Carbomix in high-dose intoxications.

Animal Studies

Several approaches have been used to demonstrate an attenuation of pharmacological or toxicological effects, poison concentration, or systemic absorption in animals treated with activated charcoal (1). Typically these studies have used a control group receiving no activated charcoal. The application of these animal findings to humans involves problems with interspecies scaling such as differences in gastrointestinal motility and morphology, absorption rate and site, dose of poison and dosage form, and metabolism and elimination rates and pathways. Nevertheless, animal studies serve to confirm *in vitro* adsorption studies by demonstrating *in vivo* reduction in a poison's effect or absorption. Many animal studies reported statistical analysis of the data comparisons; others reported data compared with a control group deemed to be sufficiently different to demonstrate a change. Direct extrapolation of the findings in animal studies to human poisoning should be done cautiously, if at all, and accordingly, few studies are reviewed in this document.

Volunteer Studies

Studies in human volunteers are based typically on the comparative bioavailability studies of a test drug using a controlled, randomized, crossover design involving six to ten participants. Measures such as the area-under-the-curve (AUC) of drug concentration versus time or the extent of recovery of the drug in urine are employed depending upon the properties of the drug. Since human volunteers are used as experimental subjects, only subtoxic doses of drugs have been studied.

Some studies have attempted to correlate *in vitro* adsorption to reduction in absorption (20,21,25,26). Although these studies serve to confirm basic principles of adsorption, the results cannot be extrapolated directly to the care of a poisoned patient.

Extrapolation of data from human volunteer studies to patients who overdose is difficult because of the following factors: 1) variations in pharmacokinetics (e.g. differing dissolution, gastric emptying, and absorption rates) seen with toxic as opposed to therapeutic doses (27); 2) variable delay in the administration of activated charcoal; and 3) differences in the adsorptive properties of activated charcoal present in the stomach of a fasting human volunteer compared with the varying stomach contents of some patients who overdose.

The results of 122 comparisons involving 46 drugs are tabulated in Appendix 1. There is considerable variation in the absolute amount of charcoal used (0.5–100 g) and the resulting gram-to-gram ratio of charcoal to drug (1:1 to 100,000:1). The time delay for the administration of the charcoal was up to 360 minutes after drug administration.

Eighty-four comparisons took place at $\leqslant 5$ minutes (Table 2). In these studies when activated charcoal was administered at 30 minutes, there was a mean reduction in absorption of 51.70% (n=7); at 60 minutes the mean reduction was 38.14% (n=16); at 120 minutes the mean reduction was 34.54% (n=8). The data from 48 comparisons involving 26 drugs using at least 50 g of activated charcoal (Table 3) showed a mean reduction in absorption of 47.3% (n=3) when activated charcoal was administered at 30 minutes after dosing; the mean reduction at 60 minutes was 40.07% (n=12), and at 120 minutes was 16.50% (n=3). These volunteer studies demonstrate that the maximum reduction in drug absorption occurs when activated charcoal is administered within 60 minutes of drug dosing.

Data from studies where activated charcoal was administered at or more that 120 minutes after dosing are given in detail below.

Impact of Activated Charcoal Administered $\geq$120 Minutes After Dosing

Yeates and Thomas (28) conducted an open, randomized, crossover four-arm study in volunteers to determine the efficacy of activated charcoal in reducing paracetamol absorption when the administration of charcoal was delayed by 1, 2, or 4 hours. Volunteers consumed a standard breakfast followed one hour later by paracetamol 3 g and no charcoal or charcoal 50 g delayed by 1–4 hours. Blood samples were obtained over a 9 hour period and statistical comparisons were made between the area under the serum concentration-time curves (AUC mcg/L-hours) values. AUCs between 4 and 9 hours showed statistically significant reductions at 1 hour (56%; $p<0.002$) and 2 hours (22%; $p<0.03$), but not at 4 hours

TABLE 2

Summary of the reduction of drug absorption by single-dose activated charcoal (0.5–100 g) in human volunteer studies (n=122 comparisons involving 46 drugs) at varying time intervals (0–360 minutes) after drug dosing

	Time (min) of administration of charcoal after drug dosing												
% Reduction in drug absorption	0–5 (n=84)	30 (n=7)	0–30 (n=92)	60 (n=16)	0–60 (n=108)	120 (n=8)	0–120 (n=117)	180 (n=3)	0–180 (n=120)	240 (n=3)	0–240 (n=123)	360 (n=1)	0–360 (n=124)
Mean	74.10	51.70	72.17	38.14	67.13	34.54	64.75	21.13	63.66	29.33	61.44	14.00	60.95
SD	27.59	14.73	27.40	20.25	29.09	26.76	30.00	16.17	30.50	20.50	30.75	0.00	30.94
Median	86.85	49.40	83.00	30.20	74.60	25.00	65.20	13.60	64.65	23.00	63.50	14.00	62.90
Max	100.00	75.00	100.00	77.90	100.00	49.60	100.00	43.60	100.00	80.00	100.00	14.00	100.00
Min	12.30	31.10	12.30	5.70	5.70	7.70	5.70	6.20	5.70	8.00	5.70	14.00	5.70

TABLE 3

Summary of the reduction of drug absorption by single-dose activated charcoal ($\geq$50 g) in human volunteer studies (n=48 comparisons involving 26 drugs) at varying time intervals (0–180 minutes) after drug dosing

	Time (min) of administration of charcoal after drug dosing										
% Reduction in drug absorption	0–5 (n=25)	30 (n=3)	0–30 (n=28)	60 (n=12)	0–60 (n=40)	120 (n=3)	0–120 (n=43)	180 (n=3)	0–180 (n=46)	240 (n=2)	0–240 (n=48)
Mean	89.83	47.30	85.27	40.07	71.71	16.50	67.86	21.13	64.82	32.50	63.47
SD	17.41	10.39	21.33	19.82	29.42	6.32	31.71	16.17	33.01	24.50	33.34
Median	97.00	40.00	96.15	30.20	83.00	20.00	78.50	13.60	76.45	32.50	73.50
Max	100.00	62.00	100.00	77.90	100.00	22.00	100.00	43.60	100.00	57.00	100.00
Min	18.30	39.90	18.30	12.90	12.90	7.70	7.70	6.20	6.20	8.00	6.20

(8%). AUCs between 0 and infinity demonstrated a significant reduction only at 1 hour (43%; $p<0.002$). The results suggest that the use of activated charcoal more than 1 hour after a paracetamol overdose is unlikely to be useful clinically.

Laine et al.(29) conducted a randomized, crossover four-arm study in volunteers to determine the efficacy of activated charcoal in reducing fluoxetine absorption when activated charcoal was administered immediately, 2 hours and 4 hours after the ingestion of fluoxetine 40 mg. The subjects were randomized into 4 groups of 8 and fasted overnight. Blood samples were drawn at 1, 2, 3, 4, 5, 6, 7, 8, 12, 24, 48, 72, and 96 hours after fluoxetine ingestion. Plasma samples were analyzed for fluoxetine and norfluoxetine. The area under the plasma-time concentration curve (AUC), peak plasma concentration and elimination half-life were used to compare the control values with the study phases. No detectable fluoxetine was found in any subject when activated charcoal was administered immediately after ingestion of fluoxetine and norfluoxetine was detected in only one subject. This demonstrated the adsorptive affinity of activated charcoal for fluoxetine. Activated charcoal was not effective in preventing the absorption of fluoxetine at 2 hours (the mean AUC was reduced by 16% and mean Cmax by 11%) or 4 hours (the mean AUC was reduced by 23% and Cmax by 12%). The mean half-life of fluoxetine in the control group was 30.5 ± 10.4 hours compared to 23.2 ± 9.0 hours and 23.0 ± 9.4 hours in the 2 and 4 hour delayed administration activated charcoal study groups, respectively. However, these values were not statistically different. The authors concluded that the immediate administration of activated charcoal completely prevented the absorption of fluoxetine and that delayed activated charcoal administration diminished its value. This study did not show a benefit of activated charcoal administration at two hours or greater after fluoxetine dosing. No conclusions can be drawn about the optimal administration time of activated charcoal since it was not administered at any interval between zero and 2 hours after the ingestion of fluoxetine.

Laine et al. (30) investigated the effect of the simultaneous administration of activated charcoal on the absorption of verapamil in human volunteers. In this study, 9 fasted subjects ingested verapamil 80 mg as the control limb. Subsequently, they ingested verapamil 80 mg followed immediately by the administration of activated charcoal 25 g. In the third limb of the study, the activated charcoal administration was delayed by 2 hours. Blood samples were obtained before verapamil ingestion and at 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, and 24 hours. Plasma samples were used to determine the area under the plasma concentration-time curve (AUC) from 0–24 hours. Other measures of effectiveness were the peak plasma concentration (Cmax) and the time to peak (tmax). The immediate administration of activated charcoal reduced verapamil absorption by 99% (control AUC 270 ± 89 ng/mL/h v. 3.9 ± 4.0 ng/ml/h; $p<0.005$). When charcoal was administered at 2 hours post-verapamil ingestion, 98% (AUC 264 ± 101 ng/mL/h) of the verapamil was absorbed demonstrating no appreciable effect of the charcoal. The Cmax was reduced by 98% (control 67 ± 31 ng/mL v. 1.1 ± 1.0 ng/mL) when charcoal was administered immediately, but the Cmax was increased by 34% when charcoal was administered following a 2 hour delay. There was no significant difference between tmax and half-life when comparing the control limb with either charcoal limb. This study demonstrated that charcoal has a high affinity for verapamil, but it has no appreciable effect upon verapamil absorption when administered two hours after its ingestion.

Laine et al. (30) investigated the effect of delayed administration of activated charcoal on the absorption of verapamil slow-release in human volunteers. Eight fasted subjects ingested verapamil slow-release 240 mg as the control limb. Subsequently, they ingested verapamil slow-release 240 mg followed immediately by the administration of activated charcoal 25 g. In the third limb of the study, the activated charcoal administration was delayed by 2 hours. Blood samples were obtained before verapamil ingestion and at 1, 2, 3, 4, 5, 6, 8, 10, 12, and 24 hours. Plasma samples were used to determine the area under the plasma concentration-time curve (AUC) from 0–24 hours. Other measures of effectiveness were the peak plasma concentration (Cmax) and the time to peak (tmax). The immediate administration of activated charcoal reduced verapamil slow-release absorption by 86% (control AUC 1132 ± 515 ng/mL/h v. 158 ± 189 ng/ml/h; $p<0.001$). When charcoal was administered at 2 hours post-verapamil ingestion, absorption was reduced by 35% (AUC 731 ± 512 ng/ml/h; $p=0.04$). When charcoal was administered at 4 hours post-verapamil ingestion, absorption was reduced statistically from control (772 ± 313 ng/mL/h; $p=0.001$). At 2 and 4 hours the Cmax was not reduced statistically when compared to control. The mean tmax was reduced by 50% at both 2 and 4 hours when compared to control. There were no statistical differences in half-life between control and any of the study limbs. The study demonstrated that charcoal has a high affinity for verapamil slow-release and the authors concluded that activated charcoal administration even 2–4 hours after the ingestion of a therapeutic dose of verapamil slow-release was effective in preventing the absorption of verapamil.

Laine et al. (31) investigated the effect of the delayed administration of activated charcoal on the absorption of pholcodine in human volunteers. A total of 32 volunteers were randomized into 4 groups of 8 subjects. This was a parallel rather than a crossover study. All subjects in each group fasted overnight prior to participation. Group 1 subjects ingested pholcodine syrup 100 mg in 50 mL and served as the control group. Group 2 subjects ingested pholcodine 100 mg and immediately thereafter, ingested activated charcoal 25 g. Group 3 subjects followed the Group 2 protocol, but charcoal administration was delayed by 2 hours. Group 4 subjects had the activated charcoal administration delayed by 5 hours and then received multiple-dose activated charcoal for 84 hours making the results of this phase irrelevant beyond the 5 hour charcoal dose. Blood samples were obtained before pholcodine ingestion and at 1, 2, 3, 4, 5, 6, 8, 10, 12, 24, 48,

72, and 96 hours. Plasma samples were used to determine the area under the plasma concentration-time curve (AUC) from 0–96 hours. Other measures of effectiveness were the peak plasma concentration (Cmax), the time to peak (tmax), and the amount of pholcodine excreted into the urine. Activated charcoal administered immediately after pholcodine ingestion reduced absorption statistically by 91% (AUC control 2403±292 ng/mL/h v. 206±282 ng/mL/h; $p<0.0005$). When charcoal administration was delayed by 2 hours, absorption reduction was still significant statistically, but reduced by 28% (AUC 1777±418 ng/mL/h; $p=0.002$). The AUC was not reduced statistically from control when charcoal administration was delayed by 5 hours. Cmax reduction of 77% (control 63±12 ng/mL v 15±14 ng/mL) was significant ($p<0.005$) following immediate charcoal administration, but not statistically different from control when charcoal administration was delayed either 2 or 5 hours. The mean tmax was reduced significantly (control 5 hours v. 1.5 hours) when charcoal was administered immediately ($p<0.01$), but there were no differences between control and the 2 and 5 hour study periods. Half-life was not different from control in any phase. The amount of pholcodine excreted in the urine was reduced statistically in the immediate and 2 hour limbs (85% [$p<0.0005$] and 28% [$p=0.004$], respectively). The authors concluded that pholcodine absorption is prevented by activated charcoal and especially when the charcoal was administered immediately after pholcodine ingestion and up to 2 hours after pholcodine ingestion.

Green et al. (32) studied the effectiveness of activated charcoal 50 g given 1, 2, and 3 hours following the administration of acetaminophen 4 g to 10 fasting volunteers. This was a randomized, controlled, 4-limb crossover study with the control limb being acetaminophen 4 g without charcoal administration. Blood samples were obtained at 0, 0.5, 1, 2, 3, 4, 6, and 8 hours after acetaminophen ingestion. Bioavailability was determined from serum acetaminophen concentrations that were used to calculate the mean±standard deviation area under the absorption curve (AUC) values. The mean AUCs of acetaminophen bioavailability at 1, 2, and 3 hours were 154±71 mg/L/h, 206±67 mg/L/h, and 204±58 mg/L/h, respectively. These values represented reductions in bioavailability at 1 hour of 30.5%, 2 hours 7.7% and 3 hours 6.2%. Only the reduction at 1 hour was statistically different from the control AUC (221±54; $p<0.01$). The authors concluded that their results did not support the administration of activated charcoal beyond 1 hour after drug overdose.

Christophersen et al. (33), using paracetamol 50 mg/kg as a marker substance, investigated the effectiveness of activated charcoal 50 g alone (at 1 and 2 hours) and the use of gastric lavage followed by activated charcoal 50 g after the ingestion of the paracetamol versus a control of no activated charcoal in 12 human volunteers. The study was a four limb randomized crossover study. All volunteers consumed a semi-solid meal prior to participating in one of the four limbs of the study. Blood samples were obtained at 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, and 7 hours after ingestion of the paracetamol. To determine paracetamol bioavailability, serum paracetamol concentrations were used to calculate the area under the absorption curve (AUC). AUCs and the percent bioavailability compared to control were calculated using median values. The median Cmax of the control was 41.8 mg/L compared to 12.28 mg/L in volunteers who received activated charcoal 1 hour after paracetamol ingestion ($p<0.05$) and 40.3 mg/L ($p=$NS) when charcoal was administered 2 hours after the paracetamol. The AUC for the control limb was 189.8 mg/L/h compared to 52.9 at 1 hour ($p<0.05$) and 151.7 at 2 hours ($p<0.05$). The median AUC at 1 hour was reduced by 66% ($p<0.005$) and the median reduction at 2 hours was 22.7% ($p<0.01$). The authors concluded that activated charcoal is most effective when administered within one hour of an overdose.

Sato et al. (34) investigated the effect of super-activated charcoal (2000 m^2/g) on the absorption of acetaminophen in a randomized, unblinded human volunteer study. Volunteers fasted overnight and then were assigned by coin-flip to the control phase (acetaminophen 2 or 3 g) or the activated charcoal (75 g) arm of the study. Forty-six of forty-eight subjects completed the study. The first 13 received acetaminophen 2 g and subsequently the subjects received acetaminophen 3 g. Activated charcoal was administered 3 hours after the acetaminophen. Serum acetaminophen concentrations were measured at 4 and 7 hours after acetaminophen administration. There was no statistical difference between the control and charcoal groups at either 4 or 7 hours in the acetaminophen 2 g experimental group. The study protocol was then changed and acetaminophen 3 g was administered to each subject. The mean±S.D. serum acetaminophen concentrations in the acetaminophen 3 g group were: at 4 hours—control 21.8±6.5 mg/L and charcoal 12.3±4.4 mg/L; at 7 hours—control 7.7 mg/L and charcoal 2.1±1.9 mg/L. The controls were statistically different from the charcoal phase values. The authors concluded that there was ''some detoxification benefit in the administration of super-activated charcoal 3 hours after an overdose.'' The study results cannot be validated due to methodological limitations: area under the time-concentration curve calculations were not performed and an unsubstantiated correction factor was used to standardize discrepancies in weight since each subject did not participate in both the control and experimental phases.

Laine et al. (35) investigated the effect of immediate and delayed activated charcoal administration on the absorption of the calcium channel blocker amlodipine in 32 human volunteers. The study subjects were randomized into 4 groups of 8 subjects using a parallel rather than a crossover design. Control group subjects ingested amlodipine 10 mg. Another group ingested the amlodipine followed immediately by activated charcoal 25 g. Activated charcoal was delayed by 2 or 6 hours in the remaining groups. Blood samples were obtained before marker drug ingestion and at 2, 4, 6, 8, 10, 12, 24, 48, 72, and 96 hours thereafter in each of the study limbs.

Plasma samples were used to quantify the area under the plasma-concentration curve (AUC), the Cmax and t max. Urine was collected for 72 hours in 24 hour fractions. When charcoal was administered immediately, amlodipine absorption reduced the AUC statistically by 98.6% (3.9±1.3 ng/mL/h v. control of 268±99 ng/mL/h; $p<0.0005$). When charcoal administration was delayed by 2 hours the AUC reduction was significant at 49.6% (138±26 ng/mL/h; $p=0.001$) when compared to control. Cmax was reduced significantly following immediate charcoal administration (0.7±0.3 ng/mL; $p<0.0005$) and when there was a 2 hour delay (4.1±0.7 ng/mL; $p<0.01$) compared to control (7.2±2.4 ng/mL). Tmax was reduced statistically only when charcoal was administered immediately. Urinary excretion was reduced significantly only when charcoal was administered immediately (control 276±100 ng v. 3±1 ng; $p<0.0005$). The authors concluded that amlodipine is adsorbed effectively by activated charcoal. When charcoal administration was delayed by 2 hours, absorption was still reduced significantly.

Kirshenbaum et al. (36) examined the value of activated charcoal in sorbitol and the role of whole bowel irrigation in a three phase randomized crossover protocol in 10 adult volunteers. Each volunteer ingested nine 325 mg doses of enteric-coated acetylsalicylic acid on three occasions, with at least one week between each administration period. Activated charcoal in sorbitol reduced the time to peak salicylic acid concentrations from 10±2 hours to 7±2 hours. In addition, charcoal in sorbitol decreased bioavailability by 57% (time 0 to 8) and by 29% (4 to 14 hours after drug ingestion).

Conclusions

The results of 122 comparisons with 46 drugs (Appendix 1) indicate considerable variation in the absolute amount of charcoal used (0.5–100 g) and the time of administration (up to 360 minutes after ingestion); 84 comparisons took place at ≤ 5 minutes (Table 2). In these studies when activated charcoal was administered at 30 minutes, there was a mean reduction in absorption of 51.70% (n=7); at 60 minutes the mean reduction was 38.14% (n=16); at 120 minutes the mean reduction was 34.54 % (n=8); at 180 minutes the mean result was 21.13% (n=3); at 240 minutes the mean reduction was 29.33% (n=3) and at 360 minutes the reduction was 14% (n=1).

The data from 48 comparisons involving 26 drugs using at least 50 g of activated charcoal showed a mean reduction in absorption of 47.3% (n=3) when activated charcoal was administered at 30 minutes after dosing; the mean reduction at 60 minutes was 40.07% (n=12); at 120 minutes was 16.50% (n=3); at 180 minutes was 21.13% (n=3); at 240 minutes was 32.50% (n=2); 25 comparisons were made at ≤ 5 minutes (Table 3).

These volunteer studies demonstrate that the effect of activated charcoal diminished as the time of administration after drug ingestion increased. These data support the potential benefit for poisoned patients if charcoal is given within one hour after the ingestion of a poison. The comparisons at two hours after drug ingestion have inconsistent results. Therefore, the potential for benefit after one hour cannot be excluded.

Impact of Activated Charcoal Dose on Efficacy and Surface Area on Adsorption

The effect of charcoal-drug ratios on the antidotal efficacy of oral activated charcoal was studied in six human volunteers (20). Using a randomized crossover design, each volunteer ingested sodium aminosalicylic (PAS) acid 1 g, 5 g, 10 g or 20 g alone as a control and the same dose followed immediately by activated charcoal 50 g. Charcoal administered after PAS 1 g reduced bioavailability by over 95%, 5 g by almost 90%, 10 g by 75% and 20 g by 63%. All values were statistically significant ($p<0.05$) compared to control.

Tsuchiya and Levy (21) studied five healthy male volunteers who were administered aspirin 1 g, salicylamide 1 g or phenylpropanolamine 50 mg. Varying amounts (0.5 g–10 g) of activated charcoal were administered and the mean percent urinary recovery of each drug was compared to control. Mean salicylate recovery in the urine was reduced significantly ($p<0.01$) to 87.4% (charcoal 1.9 g) and 60.6% (charcoal 10 g). Urine salicylamide recovery following charcoal 1.5 g was 71.8% ($p<0.01$) and 23.1% with charcoal 10 g ($p<0.01$). The percentage of phenylpropanolamine recovered in the urine after charcoal 0.5 g was 42.0% ($p<0.01$) and 5.2% ($p<0.01$) after charcoal 5 g.

Roberts et al. (37) conducted a human volunteer, prospective double-blind, crossover study to compare the effectiveness of low (950 m^2/g) versus high (2000 m^2/g) surface area activated charcoal in the prevention of acetaminophen absorption. Six fasting volunteers ingested acetaminophen 50 mg/kg followed by oral activated in an 8:1 ratio of charcoal to acetaminophen. Blood samples were obtained at 0.5, 1, 1.5, 2, 3, 4, and 5 hours post-ingestion to determine serum acetaminophen blood concentrations. The volunteers served as their own controls. Five hour area under the serum concentration-time curve (AUC) and peak acetaminophen concentrations were used for statistical comparisons. However, no data regarding AUC were presented in the study. There was a 44–85% reduction in peak acetaminophen concentrations (1.4–9.0 mg/L) with the high surface area charcoal compared to low surface area charcoal (9.2–19.2 mg/L). The authors concluded that high surface area activated charcoal was superior to low surface area charcoal. Despite the small sample size, it is apparent that high surface area charcoal is more effective than low surface area charcoal. However, no further conclusions can be drawn since there was no acetaminophen-only arm in this study.

Rangan et al. (38) investigated the adsorptive capacity of super-activated charcoal versus a super-activated charcoal-cola mixture in human volunteers who ingested a

supratherapeutic dose of acetaminophen. Eight of 12 volunteers completed this three-arm, prospective, unblinded, crossover study. Following an 8 hour fast, each volunteer ingested acetaminophen 80 mg/kg followed by water 240 ml or activated charcoal 1 g/kg mixed with water 240 ml. Blood samples were obtained at 0, 0.5, 1, 2, 4, and 6 hours after acetaminophen ingestion. Serum acetaminophen concentrations were used to calculate area under the concentration-time curves (AUC) from 0–6 hours. The AUC for control was 298.5±82.5 mg-h/L compared to 77.1±34.0 mg-h/L for the activated charcoal arm, representing a statistically significant 74.2% ($p<0.05$) reduction in absorption. The Cmax for control was 87.5±19.9 and 33.0±34.0, a statistically significant 62.2% ($p<0.05$) reduction. This study verifies that activated charcoal decreases the absorption of acetaminophen.

Clinical Studies

The twelve clinical studies designed to evaluate the effectiveness of activated charcoal can be divided into three groups: six that had charcoal in both study arms (2,4,39–42); three that had charcoal in one arm (43–45); and four that compared charcoal to a no treatment control group (2,46–48). These clinical studies have been criticized for their design (49,50) with many studies exhibiting shortcomings such as selection bias (weak randomization), no laboratory confirmation or correlation with history, insufficient number of severe cases, no control group, no quantitative measure of outcome, no stratification by severity in severe cases, no relationship to the time of ingestion for patient selection or data analysis, exclusion bias, and performance bias.

Activated Charcoal-Both Study Arms

Each of the following six studies compared activated charcoal to activated charcoal in combination with another therapy. Since activated charcoal was administered to both study groups, it is impossible to evaluate the effectiveness of activated charcoal. Nevertheless, these studies are reviewed as they are often cited in support of the clinical use of activated charcoal.

Kulig et al. (39) reported a single institution, prospective study performed which included consecutive patients with an initial diagnosis of oral drug overdose. Exclusions included spontaneous or induced emesis, antecedent ipecac administration, the ingestion of hydrocarbons, corrosives, iron, strychnine, acetaminophen (paracetamol) alone, or ethanol alone. An alternate day allocation of treatments (activated charcoal and magnesium sulfate with gastric lavage or ipecac syrup versus activated charcoal 30–50 g with magnesium sulfate 20 g) was stratified by mental status of the patient upon arrival to the emergency department. A total of 592 patients completed the study, of which 472 (79.7%) had a known time of ingestion and five (0.8%) were under five years of age. No difference was found between treatment groups based on clinical deterioration or improvement after initial emergency department assessment. In a subset of obtunded patients who received treatment within one hour of exposure, 16 out of 56 (28.6%) patients who were lavaged and given activated charcoal within one hour improved ($p<0.05$), compared to three out of 32 (9.4%) who only received activated charcoal.

Albertson et al. (40) reported a single institution, prospective study that included consecutive patients who presented to the emergency department with an oral drug overdose, were awake with an intact gag reflex, and over 18 years of age. Patients were excluded if they had a rapidly deteriorating level of consciousness, spontaneous or induced emesis, antecedent ipecac, or the poison was a drug for which ipecac was contraindicated, (e.g., an acid, a base, camphor, a volatile petroleum distillate, strychnine, iron alone, or lithium alone). Patients were assigned to a treatment group (activated charcoal and sorbitol followed by ipecac syrup 30 mL versus activated charcoal 1 g/kg with sorbitol) by hospital number. In the 200 patients completing the study, those receiving activated charcoal alone were discharged from the emergency department in significantly ($p<0.05$) less time than those receiving ipecac and activated charcoal. For the hospitalized patients ($n=25$), the duration of hospitalization, ICU admission rate, and duration of ICU stay were not statistically different between the two groups. A complication rate of 5.4% was found in the ipecac and activated charcoal group (aspiration occurred in four patients who had ingested a tricyclic antidepressant), whereas there was a complication rate of 0.9% in the activated charcoal group which was not related to the administration of activated charcoal.

Merigian et al. (2) reported a single institution, prospective study involving consecutive adults presenting to an emergency department with self-poisoning. The interval between ingestion and treatment was unknown. Exclusion criteria included vomiting or the ingestion of the following substances: lithium, iron, heavy metals, monoamine oxidase inhibitors, digoxin, formaldehyde, mushrooms, acetaminophen, methanol or sustained-release products. An alternate day allocation scheme for treatments was stratified by the presence of symptoms as assessed by clinical parameters at the time of presentation to the emergency department. Symptomatic patients ($n=357$) were assigned to receive activated charcoal 50 g preceded by gastric lavage ($n=83$) or activated charcoal 50 g preceded by ipecac versus nasogastric aspiration (until stomach contents were no longer present) and activated charcoal 50 g ($n=194$). Patients who received activated charcoal and gastric aspiration were less likely ($p<0.0001$) to be admitted to intensive care ($n=40$, 20.6%) and more likely ($p<0.0001$) to be admitted to a non-intensive care unit ($n=72$, 37.1%) compared to the group that received activated charcoal and gastric lavage and ipecac ($n=74$, 45.4%; $n=20$, 12.3%; respectively). The group that received gastric lavage or ipecac exhibited a four-fold greater rate of intubation ($p<0.0001$) and ventilator use ($p<0.0001$) compared to those who received only nasogastric aspiration and activated charcoal. Interpretation of this study is difficult

as all three treatment groups received activated charcoal and some form of gastric evacuation. No group received activated charcoal alone.

Kornberg and Dolgin (4) conducted a single institution, prospective study of consecutive pediatric patients who presented to the emergency department with an oral poisoning and were less than six years of age with a mild to moderate severity of poisoning. Exclusions included patients who were not alert or who had no definite gag reflex, those with a rapidly deteriorating level of consciousness, patients who exhibited spontaneous or induced emesis, those who had already received ipecac, patients who had ingested a corrosive, hydrocarbon, iron, ethanol alone, or acetaminophen alone, or patients who presented more than six hours after the time of ingestion. Patients were assigned to one of two treatment groups (ipecac syrup 15 mL followed by activated charcoal with sorbitol versus activated charcoal 1 g/kg with sorbitol) based on an alternate day design. Seventy patients completed the study and three (4.3%) were admitted subsequently to the hospital. An unreported number received confirmation of the history by a toxicologic screen. No differences in the outcomes were detected based on hospitalization rate and the proportion of patients who improved in the emergency department. Patients receiving ipecac syrup remained in the emergency department (4.1 ± 0.2 hr, SEM) for a longer period of time ($p<0.05$) than those who received only activated charcoal (3.4 ± 0.2 hr).

Bosse et al. (41) conducted a prospective study of 51 patients who presented to a single institution following tricyclic antidepressant overdose and had a tricyclic antidepressant drug present in a urine drug screen. Patients were assigned every third day to one treatment regimen: activated charcoal 50 g and magnesium citrate 240 mL, gastric lavage followed by activated charcoal 50 g and magnesium citrate 240 mL, or activated charcoal 25 g followed by gastric lavage and activated charcoal 25 g with magnesium citrate 240 mL. No significant differences were demonstrated among the three treatments in the endpoints studied which included tricyclic-related symptoms, such as seizures, wide QRS or hypotension, and outcome measures, such as duration of hospitalization, duration of intensive care unit stay, or time on mechanical ventilation.

Pond et al. (42) reported a single institution, prospective study that included consecutive patients who were 13 years of age and older with a history of a drug overdose. Patient exclusion criteria included ingestions occurring more than 12 hours prior to arrival, treatment that breached the protocol, and if the ingested substance was not adsorbed to charcoal. Patients who vomited spontaneously were not excluded. Based on the patient's mental status at presentation to the emergency department, treatments (ipecac syrup or gastric lavage with activated charcoal versus activated charcoal 50 g) were assigned by alternate day allocation. A total of 876 patients were included in the study which included 82 whose treatment did not adhere to the study protocol. No changes in the patients' condition or intubation rate were detected in all patients and in the subset of patients treated within six hours of ingestion. In the 30 patients treated within one hour of ingestion with activated charcoal and gastric evacuation, 13 of 21 (61.9%) patients demonstrated improvement ($p=0.02$); whereas, two out of nine (22.2%) improved after activated charcoal alone. When these data were adjusted for severity by the authors, they reported no difference in the rate of deterioration ($p=0.101$) or improvement ($p=0.151$) between the treatment groups.

Activated Charcoal–One Study Arm

These three studies included only one study arm where activated charcoal was used. Design flaws limit the clinical usefulness of the data.

Comstock et al. (43) conducted a single center prospective study of a convenience sample of 339 adults who presented to the emergency department with acute drug overdose. All patients received gastric lavage and 131 patients were chosen in an unspecified random manner to receive activated charcoal 100 g after lavage. All patients had blood samples taken at the time of lavage and some had samples taken periodically for up to 21 hours thereafter. Of the total population, 25 activated charcoal patients and 37 control patients had measurable blood concentrations of specified sedative-hypnotic drugs or aspirin and these patients constituted the initial population under study. This study population was reduced further because only 22 of 37 patients in the control group and 9 of 25 patients in the activated charcoal group had samples both in the one- to three-hour interval and in the three- to five-hour interval. There was no statistical difference between the lavage (control) group and the lavage plus charcoal group in the percentage of patients exhibiting increased blood drug concentrations. For the group of patients with moderate severity of symptoms, the mean residual blood drug concentrations declined significantly ($p<0.05$) in the charcoal-treated patients at the three- to five-hour (four patients) and five- to nine-hour (three patients) intervals compared with controls (12 and nine patients, respectively). However, the experimental design of this study and statistical analysis of the data are seriously flawed and consequently these findings cannot be interpreted reliably.

Crome et al. (44) conducted a prospective study in an unspecified number of emergency departments which included adult patients with suspected antidepressant poisoning that were going to be admitted to the hospital. Patients were randomly allocated to one of two treatment groups: activated charcoal 10 g as Medicoal (charcoal containing povidone and sodium bicarbonate) with supportive care or supportive care alone; an undetermined number of patients also under went gastric lavage. Although 48 patients entered the study, only 17 patients had taken tricyclic antidepressants alone according to laboratory analysis. The coma grade of these 17 patients was reported at intervals spanning 24 hours. There were an inadequate number of observations to make comparisons between the groups.

Hultén et al. (45) performed a four-center prospective study for an unreported period of time that consisted of consecutive patients (over 14 years of age) who presented to the emergency department after ingesting one or more of seven tricyclic antidepressant drugs. Allocation to a treatment group (gastric lavage versus gastric lavage plus activated charcoal 20 g as Medicoal) was performed by random numbers and adjusted by groups of ten. Drug concentrations and urine drug screens were determined in the patients and confirmed the history of the ingestion. A total of 77 patients (34 patients in the lavage group and 43 patients in the lavage plus charcoal group) completed the study. No statistical difference in the two treatments was detected based on the following: maximum serum drug concentration, half-life, presence of toxicity, incidence of admission or duration of stay in the intensive care unit, incidence or duration of intubation, need for ventilatory support, or duration of hospitalization. The lack of difference between the two groups might have been influenced by the small dose of activated charcoal used or the delay to administer activated charcoal after gastric lavage.

Activated Charcoal-No Treatment Control Group

At two hospitals, Underhill et al. (46) prospectively studied 60 patients who ingested acetaminophen (>15 g) within the previous four hours (mean 123 minutes, range 30–240 minutes). Patients were assigned randomly to one of the following three treatment groups at one hospital: gastric lavage, activated charcoal, or ipecac. At the other hospital, the study initially contained a fourth group receiving no treatment. However, the control arm of the study, was stopped at five patients because serum acetaminophen concentrations increased between the first and last sample in four of these five patients. Blood samples for acetaminophen were taken prior to treatment, following treatment, and at 60, 90, and 150 minutes after the first sample. Although these data were presented graphically, there was no statistical analysis of charcoal-treated versus no-treatment groups.

Merigian et al. (2) investigated the outcome in 451 asymptomatic patients who received either activated charcoal 50 g or no treatment. Although there were no statistical differences in clinical outcomes between the two groups, there was no objective confirmation that these patients had ingested a toxic dose of a substance making interpretation of this study problematic.

Buckley et al. (47) conducted a retrospective study of 981 consecutive acetaminophen-poisoned patients who were admitted over a 10 year period. Treatment was not randomized and patients received no treatment, activated charcoal 1–2 g/kg or gastric lavage followed by activated charcoal. The goal of their study was to assess the impact of gastrointestinal decontamination on the clinical outcome of acetaminophen-poisoned patients. Activated charcoal alone was used in 36% of the patients and 39% received no gastrointestinal decontamination. A variant of the Rumack-Matthew nomogram was used to assess the effectiveness of activated charcoal versus no therapy. Patients who received activated charcoal were significantly (odds ratio 0.36, 95% CI) less likely to have acetaminophen concentrations in the probable toxicity or high risk portion of the nomogram when compared to those who had no gastrointestinal decontamination. They concluded that the routine use of activated charcoal in patients presenting within two hours of ingestion was beneficial in acetaminophen-poisoned patients and that there may be minor benefits up to four hours post-ingestion. The interpretation of this study is difficult for a number of reasons. Since the dose of activated charcoal was not consistent (1–2 g/kg), those with more charcoal may have had a better outcome. The median amount of acetaminophen ingested by the 'no GI decontamination' group was 2.5 g more than the charcoal group. While the difference was not statistically significant, it could have been clinically significant. The median time to presentation was 385 minutes in the 'no treatment group' compared to 135 minutes in the charcoal treatment group and higher concentrations would be expected with such a significant temporal disparity between groups. Furthermore, the study may have lacked adequate power due to small samples between subgroups which introduced the likelihood of beta error. Thus the robustness of their finding that no difference existed between the two study groups is in question.

Merigian and Blaho (48) conducted a clinical study of 1479 self-poisoned patients who were treated in an emergency department over a 24 month period. The hypothesis of the study was that the administration of activated charcoal and supportive care were no more effective than supportive care alone without any form of gastrointestinal decontamination. Patients who ingested acetaminophen (>140 mg/kg), crack cocaine, mushrooms, volatiles, caustics, heavy metals, lithium and iron were excluded from participation in the study. An even:odd day protocol was used to allocate patients to the treatment regimen of oral activated charcoal 50 g on even days and supportive care alone on odd days. Outcome measurements included mean length of stay, mean length of intubation and a number of demographic outcome measurements that included clinical deterioration. Patients were divided into three groups: (Group 1) outpatients (n=126), (Group 2) inpatients-general medical admissions (n=153) and (Group 3) inpatients-intensive care unit admissions and each group included patients who were treated and not treated with charcoal. One significant difference was apparent in the presenting vital signs of patients: the mean heart rate was statistically (but not clinically) lower in Group 2 patients receiving charcoal (96.5±2.6 bpm) compared to those who did not receive charcoal (97.1±1.9 bpm) ($p<0.01$). In Group 3 those who received charcoal had a statistically higher heart rate (109.9±3.5 bpm) than those who did not receive charcoal (104.4±3.4) ($p<0.01$). Patients treated with charcoal had a significantly longer stay in the emergency department (6.2±3.9 hours) versus those who did not receive charcoal

(5.3±3.9 hours) ($p<0.01$). There were no statistical differences between treatment groups with regard to length of stay in the inpatient and intensive care unit admitted patients. Patients in Groups 1 and 2 who were treated with charcoal had a mean duration of intubation of 54.6 hours compared to 39.9 hours in those who did not receive charcoal. There was an apparent, but not a statistical difference between these values. Based upon the parameters that were evaluated, the authors concluded that there were no demonstrable positive effects from oral activated charcoal therapy on clinical outcome. This research supports the work of Pond et al. and others who have concluded that activated charcoal administration does not change patient outcome. It must be noted that data on the temporal separation between the ingestion and the time of charcoal administration were not included in the paper. If there were significant delays in the administration of activated charcoal, a difference between treatment and no treatment would be minimized.

Case Reports

There are numerous cases in which activated charcoal has been used as one method of gastrointestinal decontamination. These case reports are difficult to assess, because they are uncontrolled, the histories are uncertain, and other therapies are often used. Therefore, case reports have not been used to evaluate the effectiveness of activated charcoal, though, they will be used to characterize the adverse effects associated with activated charcoal.

Role of Charcoal in Reducing Absorption of Selected Agents

Boric Acid. Oderda et al. (51) conducted an *in vitro* study to determine the adsorptive capacity of activated charcoal 7.5 g, 15.0 g and 30.0 g. The mean percentage adsorbed of a one gram dose was 5.7±1.6%, 17.6±3.5% and 38.6±6.3%, respectively. The values at 15 g and 30 g were statistically different ($p<0.05$) from a control of boric acid alone.

Cathartics. Since saline cathartics are co-administered occasionally with activated charcoal, several investigations have studied the potential interaction. There are conflicting data regarding the adsorptive capacity of activated charcoal for salicylates in the presence of magnesium citrate. Czajka and Konrad (52) found that magnesium citrate diminished the adsorptive capacity for aspirin by 14.9% ($p<0.05$), whereas, Ryan et al. (53) demonstrated that significantly ($p<0.01$) more salicylate was adsorbed in the presence of magnesium citrate. Neither magnesium sulfate nor sodium sulfate demonstrated the same affinity as magnesium citrate (52,53).

The addition of sorbitol had no effect on the adsorption of acetaminophen (54), but the adsorption of aminophylline was increased ($p<0.05$) in the presence of sorbitol. Nakamura et al. (55) studied the *in vitro* adsorption characteristics of acetaminophen by activated charcoal in the presence of sorbitol. The adsorption isotherms of acetaminophen adsorption to charcoal were compared to those of mixtures of acetaminophen, charcoal and sorbitol concentrations of 5, 10, 30, and 50%. Two different activated charcoals with surface areas of 885 and 1081 m^2/g were tested. The experiments were not conducted in a simulated gastric environment. After incubation of the study agents, acetaminophen was adsorbed effectively by activated charcoal in the control phase for both charcoals. There was no statistical comparison between charcoal products, but there was an apparent enhancement of acetaminophen adsorption by the higher surface area charcoal in the control and experimental phases. At an acetaminophen equilibrium concentration 1 mg/mL, the adsorption of acetaminophen was reduced to 13–16% of control at sorbitol concentrations of 30% and 50%, respectively. Even at sorbitol 5%, the adsorption of acetaminophen was reduced to approximately 74–82% of control. The rate of removal was also affected by the presence of sorbitol. In the presence of sorbitol 5%, the rate of removal by charcoal was 75–77% of control. At a sorbitol concentration of 50%, the rate of removal by charcoal was 23–24% of control. In a model that does not simulate the gastric environment, sorbitol interfered with the adsorptive capacity of charcoal significantly. However, the relevance of these data are diminished since sorbitol should never be used alone or in conjunction with activated charcoal in the management of the poisoned patient. (See the Position Paper on Cathartics for a more complete discussion.)

Ciprofloxacin. Ofoefule and Okonta (56) and Ibezim et al. (57) studied the *in vitro* adsorptive affinity of activated charcoal for ciprofloxacin. Ciprofloxacin in concentrations of 5 and 10 mcg/mL were incubated with activated charcoal 125, 250 and 500 mg. The pH was varied using either acetic acid or sodium hydroxide to produce solutions of pH 1.2, 3.0, 8.0, and 10.0 to simulate different gastric conditions and evaluate the impact of ionization on drug adsorption. Langmuir adsorption isotherms were used to characterize the adsorption profiles. Descriptive statistics were used to report the results. Activated charcoal was an effective adsorbent at all pH values, but most effective at pH 1.2 and 3.0 where 79.7% and 81.3%, respectively, of all ciprofloxacin was adsorbed. While the *in vitro* model demonstrated a high affinity of charcoal for ciprofloxacin, it is unlikely that activated charcoal would ever be used in a ciprofloxacin overdose.

Cyanide. Andersen (58) demonstrated that charcoal 1 g could adsorb 35 mg of potassium cyanide *in vitro*. This has been interpreted as demonstrating a lack of adsorption compared to many other substances. However, as little as 200 mg of potassium cyanide is a potentially lethal dose in man, while 50 g of charcoal is a typical charcoal dose. This dose of charcoal could adsorb up to 1,750 mg of cyanide, equivalent to several lethal doses. The mortality rate in rats given potassium cyanide 35 mg/kg was reduced from 93% to 33% when a super-activated charcoal was administered immediately following exposure (59). Moreover, mortality dropped from 100% to 27% when potassium cyanide 40 mg/kg was used.

Relevance to other forms of cyanide or to the clinical situation when administration of charcoal is delayed is unknown, but it is quite likely to be relevant to other simple cyanide salts. In many cases, the rapid onset of life-threatening cyanide toxicity will obviate the usefulness of activated charcoal.

2,4-Dichlorophenoxyacetic Acid (2,4 D). Belmouden et al. (60) investigated the *in vitro* adsorption of 2,4-dichlorophenoxyacetic acid (2,4-D) by activated charcoal. The purpose of the investigation was to evaluate activated charcoal for environmental elimination purposes, not the management of human exposures. However, the results have unproven but potential implications for the management of 2,4-D ingestion patients. Two different activated charcoals with different surface areas were compared over a pH range of 1.5–9.0. Langmuir adsorption isotherms were used to characterize the adsorptive affinity of charcoal for 2,4-D. The charcoal with the larger surface area adsorbed the 2,4-D more effectively and rapidly. 2,4-D adsorption was highest at pH 2.5 which is near the pKa of 2,4-D (pH 2.64). This is expected since the ionization of a weak acid is decreased in an acidic medium. The adsorption of 2,4-D was increased in the presence of NaCl. These studies were not conducted in a simulated gastric environment.

Diethylcarbamazine. Orisakwe et al. (61) studied the effect of activated charcoal on the pharmacokinetics of diethylcarbamazine. Six volunteers participated in a randomized, crossover study. After an overnight fast the subjects ingested diethylcarbamazine 150 mg (control) or a mixture of diethylcarbamazine 150 mg and activated charcoal 7.5 g or 15 g. Blood and urine samples were obtained at 0, 1, 2, 4, 8, 12, and 24 hours after study drug administration. Serum samples were used to calculate the area under the serum concentration-time curve (AUC) for 0–24 hours. Renal clearance was calculated by dividing the amount of drug collected in the urine by the AUC. The AUC for both the 7.5 g (195.58±3.68 mcg/h/mL) and 15 g (88.63±4.27 mcg/h/mL) activated charcoal doses were reduced significantly when compared to control (428.64±9.17 mcg/h/mL). Renal clearance was reduced significantly in the 7.5 g (49.2%) and 15 g (55.7%) experimental limbs of the study when compared to control. The authors concluded that activated charcoal should be used early in the management of a poisoning due to diethylcarbamazine. It is apparent that activated charcoal has a high affinity for diethylcarbamazine, but no conclusions can be drawn about the efficacy of activated charcoal when there is a delay in its administration.

In a similar study, Orisakwe et al. (61) studied the adsorptive capacity of activated charcoal for diethylcarbamazine. Six volunteers participated in a randomized, crossover study. After an overnight fast the subjects ingested diethylcarbamazine 150 mg (control) or diethylcarbamazine 150 mg followed by activated charcoal 7.5 g or 15 g. Urine collections were obtained before and at 1, 2, 4, 8, 12, 24, 36, 48, 60, and 72 hours after study drug administration. The cumulative amount of diethylcarbamazine recovered and the percentage recovered were compared. In the control limb 70.07±4.46 mg (46.7% of the total dose) was recovered. When activated charcoal 7.5 g was administered, 22.13±2.04 mg (14.8%) was recovered and 8.10±1.23 mg (5.4%) was recovered following activated charcoal 15 g. Despite numerous 'apparent' conclusions by the authors, the evidence supports only that diethylcarbamazine is adsorbed by activated charcoal and that 15 g is superior to 7.5 g.

Doxycycline. Afonne et al. (62) investigated the affect of saline cathartics on the adsorption of doxycycline by activated charcoal and the influence of sodium chloride and sodium citrate on adsorption. The data are portrayed graphically and not in tabular form. Interpretation of the data and resultant conclusions are suspect since sodium citrate interfered with the adsorption of doxycycline at only the highest concentration of sodium citrate. The study was not conducted in a simulated gastric pH medium. The paper confirms that activated charcoal adsorbs doxycycline and that sodium chloride and citrate enhance adsorption, but the findings are irrelevant since it is unnecessary to treat doxycycline overdosage with activated charcoal.

Ethanol. Although ethanol is adsorbed by activated charcoal (17,63), studies in dogs (64) and human volunteers (65) have not demonstrated a reduction in bioavailability. It is unclear whether the presence of ethanol decreases the effectiveness of activated charcoal to adsorb other toxic substances. Neuvonen et al. demonstrated that the presence of ethanol reduced the *in vitro* adsorption of aspirin, quinidine and amitriptyline presumably because ethanol altered solubility characteristics of these drugs. These same investigators (66) gave human volunteers charcoal 50 g five minutes after the ingestion of aspirin or quinidine. The co-administration of ethanol 50 g with the drugs had no significant impact on efficacy of activated charcoal. Olkkola (67) administered lethal doses of strychnine to mice and found a decrease in mortality rates when ethanol was also present in the gastrointestinal tract. However, this lack of effect should not contraindicate the use of activated charcoal in patients who have ingested ethanol and other drugs.

Fluoxetine. Tsitoura et al. (68) conducted an *in vitro* study to determine the affinity of 2 different activated charcoal products for fluoxetine. Since fluoxetine is a basic compound, the study was conducted in simulated gastric solutions with pH values of 1.2 and 7.2. Varying concentrations (130–380 mcg/mL) of fluoxetine were used and the amount of activated charcoal was held constant at 10 mg/10 mL. The activated charcoal:fluoxetine mass ratios for studies conducted at pH 1.2 were 3.3:1–7.7:1 and at pH 7.2 the ratios were 2.7:1–4.5:1. The Langmuir isotherm model was used to assess the adsorptive properties of activated charcoal. The Langmuir plots showed correlation coefficients of 0.992–0.9997 at both pH values. The authors concluded that fluoxetine was adsorbed effectively at both pH values, but that adsorption was

significantly better at pH 7.2. This is to be expected since there is less ionization of fluoxetine at a more alkaline pH.

Atta-Politou et al. (69) conducted an *in vitro* study to determine whether polyethylene glycol (PEG) and polyethylene glycol-electrolyte lavage (PEG-ELS) solution interfered with the adsorption of fluoxetine by activated charcoal. Two different brands of charcoal were used (Merck and Carbomix). Since fluoxetine is a basic compound, the study was conducted in simulated gastric solutions with pH values of 1.2 and 7.2. PEG solutions of 1–20 mg/mL and a standard solution of PEG-ELS were combined with activated charcoal 10 mg in a total volume of 10 mL. The PEG experimental solutions were added either simultaneously with the fluoxetine and activated charcoal or in a delayed fashion. The experimental solutions were incubated at 37° for 1 hour and then the free fluoxetine concentration was determined analytically. At pH 1.2 and with a charcoal to fluoxetine ratio of 6.06:1, 98.3–98.5% of the fluoxetine was adsorbed by activated charcoal. At pH 7.2 the adsorption was similar (98.7–99.7%). When the ratio of charcoal to fluoxetine was reduced to 3.03:1, the adsorption range at pH 1.2 was 63.4–64.1% and at pH 7.2 the adsorption range was 82.6–82.8%. When PEG was added in varying concentrations, the amount of fluoxetine that was adsorbed by charcoal was reduced in as the concentration of PEG was increased. When the PEG concentration was maximal (PEG: AC=2:1), at pH 1.2 and with a charcoal to fluoxetine ratio of 6.06:1, 29.1–39.1% of the fluoxetine was adsorbed by activated charcoal. At pH 7.2 the adsorption range was 45.4–50.8%. When the ratio of charcoal to fluoxetine was reduced to 3.03:1, the adsorption range at pH 1.2 was 14.9–21.9% and at pH 7.2 the adsorption range was 44.9–46.2%. Statistical analysis was not conducted, but the data demonstrate large apparent reductions in the affinity of activated charcoal for fluoxetine in the presence of PEG. The study also shows the influence of ionization on the adsorptive capacity of activated charcoal.

Atta-Politou et al. (70) conducted an *in vitro* investigation on the adsorption rate constant and the adsorption characteristics (affinity) of activated charcoal for fluoxetine. All fluoxetine solutions and charcoal slurries were prepared in an aqueous buffered solution with a pH of 1.2 to simulate the gastric environment. Varying amounts of activated charcoal from 0.125–0.500 g were added to the fluoxetine solution. The Langmuir adsorption isotherm model was used to determine the adsorption characteristics of charcoal for fluoxetine. Descriptive statistics were used to describe the results. The apparent adsorption rate constants increased by 64.8–75.7% as the amount of charcoal increased from a minimum of 0.125 g to a maximum of 0.500 g. Similarly, the maximum adsorption capacity of charcoal for fluoxetine ranged from 254.8±1.8 to 439.8±8.5 mg/g of charcoal, demonstrating effective adsorption to activated charcoal. The authors concluded that charcoal adsorbs fluoxetine effectively and rapidly at gastric pH.

Cooney and Thomason (71) conducted an *in vitro* study to determine the affinity of activated charcoal for fluoxetine hydrochloride at gastric pH's. A stock solution of fluoxetine hydrochloride was admixed with varying (but not indicated) amounts of activated charcoal in simulated USP gastric solutions (without pepsin) with pH values of 1.2 and 7.5. The Langmuir adsorption isotherms and Freundlich equation were used to assess the affinity of charcoal for fluoxetine. Despite the fact that the pKa of fluoxetine HCl is ~9.1 and that 97.55% of fluoxetine is still ionized at pH 7.5, the adsorption of fluoxetine by charcoal at pH 7.5 was superior to the adsorption characteristics at pH 1.2. For pH values of 1.2 and 7.5, the amounts of fluoxetine adsorbed per gram of charcoal were 0.258 g and 0.330 g, respectively. Statistical analyses of the data were not conducted and no conclusions about *in vivo* applications can be extrapolated from this research.

Hydrocarbons. Activated charcoal does adsorb hydrocarbons. When charcoal 3.6 g/kg was administered after oral instillation of hydrocarbon 8 mL/kg in rats, blood concentrations of kerosene were reduced significantly at all time points, i.e. 0.5, 1, 2, 4, 8, 12 hours (72). Since the ingestion of many aliphatic hydrocarbons, such as gasoline and kerosene, is not likely to produce toxicity other than that associated with aspiration, the use of charcoal in these ingestions is typically not warranted and may cause or contribute to emesis and potential complications.

Ipecac. Activated charcoal adsorbs ipecac alkaloids (73). Despite a report that co-administration of ipecac syrup 60 mL and activated charcoal 50 g did not abate the emetic effect in poisoned patients (74), this approach is inconsistent with contemporary practice.

Iron. Gomez et al. (75) conducted a prospective, crossover, controlled volunteer study to determine if activated charcoal or an activated charcoal-deferoxamine mixture could prevent the absorption of ferrous sulfate. The control group received ferrous sulfate 5 mg/kg as a solution. The subjects in the study limb ingested activated charcoal 25 g prior to the administration of the ferrous sulfate. Serum iron concentrations from blood samples obtained prior to iron ingestion and at 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, and 24 hours post-ingestion used to calculate the area under the curve. Maximum iron concentrations were also used for comparison of efficacy. The 11 subjects were not fasted completely. There was no statistical difference in the mean AUC between the control limb (13.39±5.0 mg-hour/L) and the activated charcoal limb (10.65±3.87 mg-hour/L). No statistical difference occurred in the Cmax between control (1.50±0.36 mg/L) and the activated charcoal limb (0.94±0.23 mg/L), demonstrating that activated charcoal does not adsorb ferrous sulfate.

Chyka et al. (76) studied the *in vitro* affinity of activated charcoal for ferrous sulfate in 3 simulated gastric fluids. Iron as ferrous sulfate was incubated with a control of Simulated Gastric Fluid, USP (pH 1.5), Simulated Gastric Fluid, USP (pH 7.5) and a combination of the acidic and alkaline gastric

fluids (pH 4.5). Activated charcoal 20–120 mg in 20 mg increments was added to the 3 simulated gastric fluids in each of the experimental phases. Langmuir adsorption isotherms were used to determine the adsorptive affinity of charcoal for ferrous sulfate. There was negligible adsorption of iron by charcoal at pH 1.5 (−0.01±0.26 g iron/g charcoal). At pH 4.5 (102.96±4.49 g iron/g charcoal) and 7.5 (100.94±19.02 g iron/g charcoal) charcoal had statistically significant adsorptive affinity for iron. The authors suggested that there may be a role for the use of activated charcoal in the management of iron poisoning. However, in an overdose there may be a significant delay between iron ingestion and activated charcoal administration and the charcoal may not come into contact with the iron in the more alkaline environment of the small intestine. While there is *in vitro* evidence that activated charcoal adsorbs iron, there are no data to support this in an *in vivo* model.

Isoniazid. Ofoefule et al. (77) conducted a study in five male rabbits to determine the *in vivo* adsorption of isoniazid to activated charcoal. Non-fasted rabbits were administered an oral dose of isoniazid 5 mg/kg in the control phase. After a one week washout period, isoniazid 5 mg/kg was administered and followed immediately with activated charcoal 1 g/kg. In both study limbs, blood samples were obtained prior to isoniazid administration and at 0.5, 1, 2, 3, 4, 5, 6, 7, and 24 hours after ingestion of the isoniazid. Area under the absorption curve (AUC_{0-24h} and AUC_8) was used to measure the extent of isoniazid absorption and Tmax and Cmax were used to evaluate the rate of bioavailability. The data were not analyzed for statistical significance. There were large apparent differences between the control (150.8±13.34 AUC_{0-24h} and 180.80±13.34 AUC_8) and the isoniazid and activated charcoal limbs (60.42±5.66 AUC_{0-24h} and 64.99±5.66 AUC_8) that demonstrated a high affinity of charcoal for isoniazid. There was no difference between the Tmax (2.0 hours) of either limb. There was an apparent difference between the Cmax of the two limbs (isoniazid 14.70±1.15 hours; isoniazid and charcoal 7.53±0.25 hours). While there was no statistical validation of the data, it appears that isoniazid is adsorbed *in vivo* by activated charcoal as established previously *in vitro* (77).

Lithium. Favin et al. (78) demonstrated no appreciable adsorption of lithium at acidic pH. Linakis et al. (79) gave lithium chloride 250 mg/kg and activated charcoal 6.7 g/kg to rats and found no difference in serum concentrations of lithium compared with control.

***N*-acetylcysteine.** Activated charcoal adsorbs *N*-acetylcysteine *in vitro* (54,80–82). Adsorption isotherms were used to calculate activated charcoal adsorption of *N*-acetylcysteine at pH 7.5 (80). In simulated gastrointestinal fluid and nonbiologic fluid mediums, *N*-acetylcysteine was adsorbed by activated charcoal, 746.9±214.5 mg NAC/g AC and 4626.7±386.6 mg NAC/g AC respectively. There was a significant ($p<0.01$) difference in adsorption to charcoal between the two fluids.

Klein-Schwartz and Oderda (81) demonstrated that activated charcoal 3 g adsorbed 54.6±9.4% and 6 g adsorbed 96.2±4.3% of a 200 mg/L *N*-acetylcysteine solution ($p<0.01$). Rybolt et al. (82) mixed N-acetylcysteine (3.26 mg/mL) with carbon powder 0.1, 0.2, 0.3, 0.4, 0.5 g at pH 1.2 and 7.0. At pH 1.2 the percentage adsorbed was 9.3, 20.7, 27.1, 47.6 and 53.7%, respectively. At pH 7.0 the percentage adsorbed was 23.7, 45.6, 60.8, 72.6, and 77.2%, respectively. Van de Graff et al. (54) determined that *N*-acetylcysteine decreased the adsorptive capacity of two different activated charcoals by 12–18%.

Studies in human volunteers following administration of *N*-acetylcysteine 140 mg/kg, demonstrated no decrease in bioavailability with charcoal doses of 50 or 60 g (83,84); however, the AUC was reduced by 39% ($p<0.001$) with 100 g of charcoal (85). The serum concentrations in these studies were highly variable and difficult to interpret (86).

Tenenbein et al. (87) conducted an *in vitro* study to determine whether the presence of *N*-acetylcysteine reduced the ability of activated charcoal to adsorb acetaminophen and salicylic acid. Saturated solutions of acetaminophen and salicylic acid were incubated with charcoal in solutions with pH values of 1.8 and 7.4. Charcoal ratios of 5:1 and 10:1 were used to simulate clinically relevant situations. *N*-acetylcysteine was added to the incubating solutions in amounts that were 1 to 8 times the concentration of the acetaminophen. For the 5:1 charcoal:acetaminophen concentration, binding of acetaminophen was 91.0% and 90.6% at pH 1.8 and 7.4, respectively. In the presence of *N*-acetylcysteine, the binding of acetaminophen was reduced significantly to 86.6% and 89.6% at pH 1.8 and 7.4, respectively. When *N*-acetylcysteine was present at 8 times the amount of acetaminophen, acetaminophen binding was reduced to 78% and 82% at pH 1.8 and 7.4, respectively. The presence of *N*-acetylcysteine reduced salicylic acid binding statistically, but the results were presented graphically, not in a tabular format. The study demonstrated that *N*-acetylcysteine could compete for charcoal binding sites and reduce acetaminophen and salicylic acid binding in a statistically significant fashion. However, the clinical significance of the reduction does not appear to be noteworthy. The authors concluded that the study should be conducted in an *in vivo* model to determine if the interaction is relevant.

The widespread use of intravenous acetylcysteine internationally and most recently in the United States, eliminates concerns about activated charcoal-acetylcysteine interactions.

Oxytetracycline. Alegakis et al. (88) studied the *in vitro* adsorption of oxytetracycline by activated charcoal. This study has veterinary implications and no pertinent application to the management of the poisoned patient. Animals are treated routinely with antibiotics such as oxytetracycline for prophylactic antimicrobial purposes. Activated charcoal is often used in veterinary practice as an adsorbent against microbial toxins and in many microbial diarrheal diseases. Activated charcoal was incubated with oxytetracycline at pH 2.35 and the

Langmuir adsorption isotherms were used to characterize the adsorptive affinity. More than 85% of the oxytetracycline was adsorbed within 45–50 minutes. There is no clinical relevance since activated charcoal would not be used to treat an overdose of oxytetracycline.

Paraquat and Diquat. Nakamura et al. (89) studied the in vitro adsorption characteristics of varying particle sizes (mesh) of activated charcoal for paraquat and diquat. Activated charcoal 500 mg was admixed with each of the 4 different charcoal mesh sizes and incubated for 48 hours at 37°C. Using the Freundlich equation, adsorption isotherms were calculated. Activated charcoal bound both paraquat and diquat and particle size did not influence the adsorptive capacity of the charcoal. Paraquat was adsorbed in greater quantity than diquat. This was attributed to diquat being a more polar compound. The authors suggested that charcoal with a smaller particle size would adsorb paraquat and diquat more rapidly and that should be considered when choosing which charcoal product to use in paraquat and diquat poisoning emergencies. No statistical analyses were conducted to determine if particle size affected either adsorptive capacity or the rate of adsorption onto activated charcoal. Therefore, the study results may be used only to suggest that charcoal adsorbs both paraquat and diquat.

Idid and Lee (90) administered paraquat orally to rabbits to determine whether activated charcoal would prevent the absorption of paraquat. Groups of six anesthetized rabbits received a nonfatal dose of paraquat 20 mg/kg (control) or paraquat and activated charcoal 22.5% w/v (4.5 g) given at 30 minutes or two hours after the paraquat. Blood samples were obtained at 0.5, 1, 2, 4, 8, and 24 hours after paraquat administration. Area under the concentration-time curves were used to compare the control and experimental limbs of the study. Charcoal administration at 30 minutes reduced paraquat absorption statistically by 46.5%. Charcoal administration at two hours reduced paraquat absorption statistically by 38.8%. There was no apparent difference between the activated charcoal at 30 minutes and two hour groups. The authors concluded that activated charcoal is an effective adsorbent in the treatment of paraquat poisoning and that charcoal may still be efficacious when administered more than one hour post-ingestion. However, the results of the investigation must be tempered because a nonfatal amount of paraquat was used. Furthermore, the animals were anesthetized and that may have influenced gastrointestinal emptying and given the appearance that charcoal is effective even when administered in a delayed fashion.

Rifampicin. Orisakwe et al. (91) studied the adsorptive capacity of activated charcoal for rifampicin. Six volunteers participated in a non-randomized study. After an overnight fast the subjects ingested rifampicin 600 mg (control). One and two weeks later, rifampicin 600 was administered and followed immediately by activated charcoal 7.5 g and 15 g, respectively. Urine collections were obtained before and at 1, 2, 4, 8, 12, 24, and 36 hours after rifampicin and rifampicin plus activated charcoal administration. The cumulative amount of diethylcarbamazine recovered and the percentage recovered were compared. In the control limb 78.70±2.34 mg (13.1% of the total dose) was recovered. When activated charcoal 7.5 g was administered, 24.96±2.02 mg (4.2%) was recovered and 7.40±1.30 mg (1.2%) was recovered following activated charcoal 15 g. The charcoal limbs demonstrated a statistical reduction in the absorption of rifampicin when compared to control. The evidence supports that rifampicin is adsorbed by activated charcoal and that activated charcoal 15 g appears to be superior to 7.5 g.

Thallium. Hoffman et al. (92) studied the affinity of activated charcoal for thallium in an *in vitro* model. Activated charcoal was added to a stock solution of thallium acetate in charcoal to thallium ratios of 1.5:1 to 100:1. Adsorptive affinity was defined by plotting the Langmuir isotherms. The maximal adsorptive capacity of charcoal was 59.7 mg of thallium per gram of activated charcoal. Contrary to conventional wisdom that low molecular weight metals are not adsorbed by charcoal, this *in vitro* model demonstrated statistically similar adsorptive affinity to that of the standard intervention, Prussian blue.

Tramadol. Raffa et al. (93) investigated the *in vitro* adsorption of tramadol hydrochloride by activated charcoal. A stock solution of tramadol hydrochloride was prepared in an acidic buffer solution and incubated with activated charcoal. Using the Langmuir adsorption isotherm equation it was determined that there was a direct relationship between the effectiveness of charcoal adsorption and the amount of activated charcoal present. In another phase tramadol 50 mg pharmaceutical tablets (2, 4, 8, 16, 32, 62, and 100 tablets) were pulverized in a mortar and suspended in the same buffer solution. A slurry of activated charcoal 50 g adsorbed 100% of 62 tablets and 94.6% of 100 tablets. This *in vitro* model demonstrated that activated charcoal adsorbs tramadol effectively.

Raffa et al. (93) also investigated the *in vivo* adsorption of tramadol in a murine model. The effectiveness of activated charcoal was measured by assessing the anti-nociception of the mice and overall lethality. The control group received tramadol in sterile water via oral gavage and the experimental group received a mixture of tramadol and activated charcoal. The mice in the experimental group had significantly less effect on anti-nociception compared to the control group. When lethality was used as a measure of activated charcoal effectiveness, the charcoal group had a significantly greater mean LD_{50} (2.3960 mmol/kg) than the control group (1.2863 mmol/kg). Activated charcoal was effective in reducing the toxicological effects of tramadol in mice.

Indications

Volunteer studies suggest that activated charcoal is more likely to reduce poison absorption if it is administered within one hour of ingestion. In the absence of satisfactorily designed

clinical studies demonstrating benefit from its use, the administration of activated charcoal may be considered if a patient has ingested a potentially toxic amount of a poison up to one hour following ingestion. The potential for benefit after one hour cannot be excluded.

Dosage Regimen

The wide range of the gram-to-gram ratios of charcoal: drug (1:1 to 100,000:1) in human volunteer studies (Appendix 1) makes it difficult to infer the optimal dose of activated charcoal. Moreover, these experimental studies were performed on fasted subjects, who ingested a known quantity of drug, circumstances that are not commonly encountered in poisoned patients.

The *United States Pharmacopeia* (USP DI, 2003) recommends the following oral dosage regimen.

Children up to one year of age: 10–25 g or 0.5–1.0 g/kg
Children 1 to 12 years of age: 25–50 g or 0.5–1.0 g/kg
Adolescents and adults: 25 to 100 g

Although dosing by body weight is recommended for children, there are no data or scientific rationale to support this recommendation.

Contraindications

Activated charcoal is contraindicated if the patient has an unprotected airway, such as in a patient with a depressed state of consciousness without endotracheal intubation. Activated charcoal is also contraindicated if its use increases the risk and severity of aspiration (e.g., a hydrocarbon with a high aspiration potential). Patients who are at risk of gastrointestinal hemorrhage or perforation due to pathology, recent surgery or medical conditions could be further compromised by single-dose activated charcoal. Presence of activated charcoal in the gastrointestinal tract may obscure endoscopic visualization, but a corrosive is not a contraindication when charcoal is used for co-ingested agents that are systemic toxins.

COMPLICATIONS

Considering the widespread use of single-dose activated charcoal, there are relatively few reports of activated charcoal-related adverse effects in the literature. The majority of the adverse events were not related to the appropriate use of activated charcoal, but were a complication of aspiration or the direct administration of charcoal into the lung. In particular, there were no reports of gastrointestinal obstruction or hemorrhagic rectal ulceration associated with single-dose activated charcoal.

Sato et al. (94) conducted a randomized, volunteer study to assess the effect of activated charcoal on acetaminophen absorption. Adverse effects due to charcoal were examined as sub-group analysis of the primary study (94). Twenty-four adult volunteers participated. No adverse effects were experienced by 30%. Constipation/abdominal fullness occurred in 46%, nausea 17%, headache 13%, vomiting 8%, diarrhea 8%, anal irritation 8% and drowsiness/fatigue 8%. Constipation is a often-cited but rarely encountered adverse effect of activated charcoal. Unfortunately, constipation was not defined and it was grouped with abdominal fullness, so the actual occurrence is unknown. The sample-size is too small to draw any meaningful conclusions from this study.

In four reports with activated charcoal as a treatment arm, no complications were noted (2,39,43,45). In patients receiving activated charcoal and sorbitol, Pond et al. (42) observed an overall complication rate of 3.6% (10 /274) in alert patients and a rate of 18.8% in obtunded patients (25/133). However, there was no significant difference in the rate of complications observed in those who received gastric emptying (gastric lavage and activated charcoal with sorbitol or ipecac and activated charcoal with sorbitol) versus activated charcoal alone, irrespective of whether the patients were alert or obtunded and regardless of the time from ingestion to presentation. Pulmonary aspiration occurred in 1.7% (7/407) of patients who received only activated charcoal with sorbitol, but the contribution of activated charcoal alone was unclear.

Respiratory Complications

In a clinical study of tricyclic antidepressant overdoses (41), two of 22 patients (9.1%) aspirated. Five cases of pulmonary aspiration following single-dose activated charcoal have been described (95–99).

An alert 8-month-old girl received ipecac syrup followed by activated charcoal 9 g in 35 mL of water via a nasogastric tube (95). She vomited charcoal, became cyanotic and cardiorespiratory resuscitation was initiated. Direct laryngoscopy revealed a trachea occluded with charcoal. After an eleven-day hospital course, she was discharged with normal chest radiographs and physical examination.

A 25-year-old male ingested alcohol and methaqualone (96). He was obtunded in the emergency department where he received gastric lavage and activated charcoal via an Ewald tube. He developed tension pneumothorax and a subsequent charcoal empyema probably as a consequence of gastric lavage-induced esophageal perforation. In addition, charcoal was observed in his sputum. After treatment with antibiotics he was discharged from the hospital without any symptoms.

A 16-year-old female ingested nortriptyline and was described as combative (97). She was lavaged and charcoal 75 g was administered via nasogastric tube. Ten minutes later she had a grand mal seizure and a cardiac arrest. Following development of a right-sided pneumothorax, bronchoscopy revealed charcoal staining of both mainstem bronchi. She died many weeks later and at autopsy charcoal deposition was apparent throughout the airways and bronchiolitis obliterans was present. Subsequent to this case report, a study was conducted in rats to determine if chronic non-specific airway inflammation caused by activated charcoal could produce

obliterative bronchiolitis (100). The study demonstrated that progressive airway injury could occur from charcoal and produce obliterative bronchiolitis-like lesions.

A 30-year-old male had a depressed level of consciousness following an amitriptyline overdose (98). Activated charcoal was instilled through the nasogastric tube which was in the right mainstem bronchus resulting in a decrease in oxygen saturation, wheezing, and subsequent ARDS. Bronchoscopic suctioning of the lungs returned copious amounts of charcoal. He was extubated after nine days.

A 51-year-old male had activated charcoal administered inadvertently into his right lung and pleural cavity following a salicylate overdose. The patient survived both the salicylate overdose and the therapeutic insult from activated charcoal. Charcoal-colored fluid drained from a thoracostomy tube for eight weeks. He was discharged and died four days later after another untreated salicylate overdose. The autopsy revealed the presence of a charcoal-laden sterile empyema in his right hemithorax and the microscopic presence of black material in his lung parenchyma. Death was consistent with salicylate poisoning (the post-mortem salicylate concentration was said to be 2600 mg/L) and there was no evidence that charcoal contributed directly to his demise (101).

An inebriated and incarcerated 37-year-old female was administered activated charcoal in the pre-hospital setting. The nasogastric tube had been placed in the right mainstem bronchus and penetrated the pleura resulting in the development of pneumothorax. Approximately 500 mL of activated charcoal was drained via a thoracostomy tube. The patient recovered without complications (102).

After multiple attempts, a 19-year-old female was lavaged following an ibuprofen overdose. Activated charcoal was administered via the lavage tube and shortly thereafter she experienced respiratory difficulty. An X-ray showed a widened mediastinum, pneumopericardium and subcutaneous emphysema that was consistent with esophageal perforation. Mediastinal inflammation developed and was thought to be due to the presence of both gastric contents and the charcoal-sorbitol mixture. The patient was discharged after 14 days (103).

A 19-month-old male ingested an unknown quantity of European elderberries and activated charcoal 13 g was administered via a gastric tube. The child became cyanotic immediately following inadvertent bronchial administration of the charcoal. Respiratory failure resolved after tracheal aspiration of the charcoal. The child was discharged 12 days later and at four months, no neurological or respiratory complications were present (104).

A 4-year, 11-month-old asthmatic female was given activated charcoal via a nasogastric tube after ingesting an unknown pill. The nasogastric tube was placed inadvertently into the trachea necessitating intubation and mechanical ventilation for five days. The child developed a chronic long-term inflammatory response that was deemed through biopsies to be independent of her pre-existing asthma conditions (105).

From case reports, Arnold et al. (106) associated pulmonary edema as a consequence of activated charcoal aspiration and conducted an animal study to determine if the presence of charcoal affected the pulmonary microvasculature and was responsible for the development of pulmonary edema. Charcoal was introduced into harvested, perfused rat lungs and into the lungs of living animals. The investigation demonstrated that the charcoal produced an increase in lung microvascular permeability. However, the authors also concluded that a number of other factors may have contributed to the problem as well.

Following an ingestion of tetracycline, a 20-year-old male received pre-hospital care that included placement of a nasogastric tube (99). The patient vomited and pulled out the tube. The tube was replaced and activated charcoal was administered. Sorbitol was administered subsequently in the emergency department and the patient was released. The next day he returned in respiratory distress and required intubation. Endotracheal aspiration revealed charcoal-laden mucous. He recovered uneventfully.

Pulmonary aspiration associated with inadequate airway management and following lavage in an obtunded patient should not be considered a complication or an adverse effect of charcoal, as charcoal does not cause the aspiration. When aspiration does occur following the administration of charcoal, it is difficult to attribute subsequent pulmonary problems to the charcoal as opposed to the gastric contents. Aqueous activated charcoal in the gastric aspirate probably does not increase the complication rate of aspiration, though the inclusion of povidone increases pulmonary complications (3). Fungal contamination of activated charcoal (107) may complicate pulmonary aspiration, but this problem of contamination is rare and isolated. The complications following aspiration of activated charcoal *per se* are consistent with those following the aspiration of gastric contents.

Corneal Abrasions

Two combative patients had charcoal spilled on their eyes during administration and developed transient corneal abrasions that resolved without complications (6).

Intubation/Endoscopy Difficulty

While not an adverse reaction associated with activated charcoal, charcoal discoloration of upper airway impeded visual intubation of a patient who was being treated for a tricyclic antidepressant overdose (108).

A 75-year-old female with a past medical history that included the use of activated charcoal to treat a tricyclic antidepressant overdose was found to have aggregates of activated charcoal in her distal esophagus and stomach during endoscopy for an unrelated medical problem. It was thought that the charcoal became entrapped in mucosal tears that occurred as a consequence of traumatic intubation. There were no sequelae that could be attributed to the presence of the activated charcoal (109).

Emesis

There are few reports of emesis as a complication of charcoal administration. In a report of the pre-hospital use of charcoal without sorbitol, one of 14 patients vomited (110). In a series of 20 patients who had ingested acetaminophen, three (15%) vomited after activated charcoal (46). The addition of sorbitol increased the rate of emesis to 16% (4) and 56% (5) in two other studies. The influences of rate and volume of administration, ingested toxins, and premorbid conditions are unknown.

Boyd and Hanson (111) conducted a clinical trial to determine if the rate of vomiting associated with two different activated charcoal 50 g products differed. The study was a controlled single-blind, randomized trial that was conducted in 97 sequential patients seen in an emergency department. A slurry of one product was prepared with water 400 mL. The other product was premixed to a total volume of 240 mL. Neither product contained sorbitol. Vomiting after charcoal ingestion occurred in a mean of 7% of patients. The incidence of vomiting in patients who ingested the 400 mL product was 6% and 8% with the 240 mL product. No data were presented regarding the occurrence of other associated adverse effects.

Fischer and Singer (112) conducted a randomized, double-blind trial that compared subject tolerance to a standard USP activated charcoal (control) and a super-activated granular product. Neither product contained sorbitol. Sixty-one subjects were randomized to the control or experimental group and ingested activated charcoal 60 g in each limb. The control product was ingested by 29 subjects and the experimental product by 31. Data from one subject were incomplete. Five (16.6%) subjects from the control group vomited compared to 2 (6.5%) from the experimental group. None of the subjects aspirated nor were any other adverse events attributable to either activated charcoal product.

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Appendix 1. Randomized controlled trials of single-dose activated charcoal in human volunteers

Drug (dose)	Dose	n=	Activated charcoal			Mean (±SD) bioavailability[c,d]			
			Dose (g)	Form[a]	Delay[b] (min)	Control	Charcoal	Per cent reduction[e]	Ref.
Acetaminophen	1000 mg	8	10	1	0	89.6±10.7	56.5±24.3‡	36.9[A]	(113)
Acetaminophen	1000 mg	5	5	1	0	83.0	43.8‡	47.2[A]	(114)
Acetaminophen	1000 mg	5	10	1	0	83.0	32.0‡	61.4[A]	(114)
Acetaminophen	1000 mg	5	10	1	30	83.0	57.2†	31.1[A]	(114)
Acetaminophen	3000 mg	10	50	1, 4	60	119.41	88.92*	25.5	(115)
Acetaminophen	1000 mg	6	50	2	5	100	15†	85.0[B]	(116)
Acetaminophen	1000 mg	6	50	2	30	100	60*	40.0[B]	(116)
Acetaminophen	80 mg/kg	8	1 g/kg	3	0	0.2995±0.082	0.077±0.034	74.2	(38)
Acetaminophen	4000 mg	10	50	3	60	0.221±0.054	0.154±0.071	30.5	(32)
Acetaminophen	4000 mg	10	50	3	120	0.221±0.054	0.206±0.067	7.7	(32)
Acetaminophen	4000 mg	10	50	3	180	0.221±0.054	0.204±0.058	6.2	(32)
Acetaminophen	2000 mg	13	75	2	180	8.8±3.6	7.6±3.1	13.6	(34)
Acetaminophen	3000 mg	33	75	2	180	21.8±6.5	12.3±4.4	43.6	(34)
Acetaminophen	3000 mg	10	50	3	60	0.063	0.023	56	(117)
Acetaminophen	3000 mg	10	50	3	120	0.063	0.044	22	(117)
Acetaminophen	3000 mg	10	50	3	240	0.063	0.051	8	(117)
Acetaminophen	50 mg/kg	12	50	3	60	0.190	0.053	72.1	(33)
Acetaminophen	50 mg/kg	12	50	3	120	0.190	0.152	20	(33)
Aminophylline	350 mgSR	6	50	2	5	100	19†	81.0[B]	(116)
Aminophylline	350 mgSR	6	50	2	30	100	25*	75.0[B]	(116)
Amiodarone	400 mg	6	25	2	0	6.82±0.82[H]	0.16±0.05‡	97.7	(118)
Amiodarone	400 mg	6	25	2	90	6.82±0.82[H]	3.40±1.0*	50.1[I]	(118)
Amitriptyline	75 mg	6	50	2	0	3.91±0.51[E,H]	Unmeasurable‡	100.0	(119)
Amlodipine	10 mg	8	25	3	0	268±99[D]	3.9±1.3[D]	98.6	(35)
Amlodipine	10 mg	8	25	3	120	268±99[D]	138±26[D]	49.6	(35)
Amlodipine	10 mg	8	25	3	360	268±99[D]	229±50	14.0	(35)
Ampicillin	5000 mg	10	50	3, 5	60	50.2±10.7[H]	21.8±2.4†	56.6	(120)
Atenolol	100 mg	7	25	2	5	9.05±0.67[H]	0.81±0.10*	91.0	(121)
Carbamazepine	400 mg	5	50	2	<5	258±15[H]	<10*	100.0	(122)
Carbamazepine	400 mg	5	50	2	60	258±15[H]	153±33*	40.7	(122)
Carbamazepine	400 mg	6	8	2	<5	165±3.7[H]	11±4.7*	93.3	(123)
Chloroquine	500 mg	6	25	2	<5	7.27±0.825[E,H]	0.062±0.046†	99.1	(124)
Chlorpropamide	250 mg	6	50	2	5	2581±207[H]	12.7±3.8‡	99.5	(125)
Cimetidine	400 mg	7	50	2	5	8.25±0.85[H]	Unmeasurable†	100.0	(126)
Ciprofloxacin	500 mg	6	1	4	<5	13.36±3.98	12.02±3.19	10.0	(127)
Diethylcarbamazine	150 mg	6	7.5	3	0	0.428±0.009	0.196±0.004	49.2	(61)

(*continued*)

Appendix 1. Continued

Drug (dose)	Dose	n=	Activated charcoal			Mean (±SD) bioavailability[c,d]			
			Dose (g)	Form[a]	Delay[b] (min)	Control	Charcoal	Per cent reduction[e]	Ref.
Diethylcarbamazine	150 mg	6	15	3	0	0.428±0.009	0.088±0.004	55.7	(61)
Digoxin	0.25 mg	6	8	2	<5	14.3±1.3[D,H]	0.2±0.1*	98.6	(123)
Digoxin	0.50 mg	6	50	2	<5	36.4±4.3[D,H]	2.8±11†	92.3	(128)
Digoxin	0.50 mg	6	50	2	60	36.4±4.3[D,H]	25.6±2.2*	29.7	(128)
Diphenhydramine	50 mg	6	50	2	5	757±366[D]	Unmeasurable*	100.0	(25)
Diphenhydramine	50 mg	6	50	2	60	757±366[D]	575±273	24.0	(25)
Disopyramide	200 mg	6	2.5	2	<5	38.8±7.8[H]	15.9±3.5*	59.0	(129)
Disopyramide	200 mg	6	10	2	<5	38.8±7.8[H]	4.2±1.9*	89.2	(129)
Disopyramide	200 mg	6	25	2	<5	38.8±7.8[H]	1.4±0.6*	96.4	(129)
Disopyramide	200 mg	6	50	2	<5	38.8±7.8[H]	1.4±0.6*	96.4	(129)
Disopyramide	200 mg	6	2.5	2	<5	30.1±2.2[H]	6.8±1.8*	77.4	(66)
Fluoxetine	40 mg	8		3	0	762±360	0	100	(29)
Fluoxetine	40 mg	8		3	120	762±360	641±327	16	(29)
Fluoxetine	40 mg	8		3	240	762±360	583±234	23	(29)
Furosemide	40 mg	6	8	2	<5	3.5±0.57[H]	0.03±0.02*	99.1	(123)
Glipizide	10 mg	6	8	2	0	1830±267[D,H]	352±128†	80.8	(130)
Iron	5 mg/kg	11	25	3	0	133.9±50	106.5±38.7	20.4	(75)
Indomethacin	50 mg	6	2.5	2	<5	8.9±1.5[H]	3.1±0.6*	65.2	(129)
Indomethacin	50 mg	6	10	2	<5	8.9±1.5[H]	1.3±0.3*	85.4	(129)
Indomethacin	50 mg	6	25	2	<5	8.9±1.5[H]	0.8±0.2*	91.0	(129)
Indomethacin	50 mg	6	50	2	<5	8.9±1.5[H]	0.5±0.2*	94.4	(129)
Isoniazid	600 mg	4	10	6	0	46.3	34.3	25.9	(131)
Isoniazid	10 mg/kg	3	60	1	0	100	Unmeasurable*	100.0[B]	(132)
Mefenamic acid	500 mg	9	2.5	6	60	1.843±715	1.180±551‡	36.0	(133)
Mexiletine	200 mg	6	25	2	<5	2.82±0.37[H]	0.10±0.05	96.5	(134)
Mexiletine	200 mg	6	25	2	60	2.82±0.37[H]	2.66±0.33	5.7	
N-acetylcysteine	140 mg/kg	21	100	1	30	5,799±1,756[G]	3,484±1,398‡	39.9	(85)
N-acetylcysteine	140 mg/kg	6	60	1	0	3,019±1,244	2,466±936	18.3	(84)
Phenylbutazone	200 mg	5	50	2	<5	1647±122[H]	30±10*	98.2	(122)
Phenylbutazone	200 mg	5	50	2	60	1647±122[H]	1154±267*	29.9	(122)
Phenylpropanolamine	50 mg	7	25	2	5	1.62±0.20[H]	0.57±0.07*	64.8	(121)
Phenylpropanolamine	50 mg	4	0.5	1	0	80.0	42.0†	47.5[A]	(21)
Phenylpropanolamine	50 mg	4	5	1	0	80.0	5.2†	93.5[A]	(21)
Phenytoin	500 mg	6	50	2	<5	357±35[H]	2.8±2.2*	99.2	(128)
Phenytoin	500 mg	6	50	2	60	357±35	79±17*	77.9	(128)
Pholcodine	100 mg	8	25	3	0	2403±292[D]	206±282[D]	91	(31)
Pholcodine	100 mg	8	25	3	120	2403±292[D]	1777±418[D]	28	(31)
Pindolol	10 mg	7	50	2	5	0.431±0.065[H]	Unmeasurable*	100.0	(126)

Piroxicam	20 mg	6	50	3	5	321.4±96.0[F]	6.7±7.3*	97.9	(135)
Propoxyphene	130 mg	6	50	2	5	3.65±0.43[F,H]	0.15±0.05‡	95.9	(136)
Quinidine	200 mg	6	50	2	5	17.6±0.8[H]	Unmeasurable*	100.0	(66)
Rifampicin	600 mg	6	7.5	3	0	78.70±2.34[C]	24.96±2.02[C]	68.3	(91)
Rifampicin	600 mg	6	15	3	0	78.70±2.34[C]	7.40±1.30[C]	90.6	(91)
Salicylamide	1000 mg	4	1.5	1	0	92.5	71.8†	22.4[A]	(21)
Salicylamide	1000 mg	4	10	1	0	92.5	21.4†	76.9[A]	(21)
Salicylamide	750 mg	5	5	3	5	79	47	40.5[A]	(9)
Salicylate	975 mg	4	20	2	<5	100	38.7±10.5‡	61.3[A]	(137)
Salicylate	1000 mg	7	25	2	5	695±66[H]	298±20*	57.1	(121)
Salicylate	1000 mg	6	50	2	<5	729±72[H]	109±28†	85.0	(128)
Salicylate	1000 mg	6	50	2	60	729±72	546±53*	25.1	(128)
Salicylate	1000 mg	6	25	2	<5	940±74[H]	218±29*	76.8	(134)
Salicylate	1000 mg	6	25	2	60	940±74[H]	701±113*	25.4	(134)
Salicylate	500 mg	6	2.5	2	<5	443±55[H]	309±42*	30.2	(138)
Salicylate	650 mg	3	50	2	<5	456±83	97.9±36*	78.5[C]	(139)
Salicylate	972 mg	8	20	4	<5	91.7±4.7	62.3±18.4*	32.1[A]	(140)
Salicylate	975 mg	8	10	3	0	94.2±6.1	73.8±6.1‡	21.7[A]	(141)
Salicylate	975 mg	6	15	1	30	846.5±293.0	428.2±218.6†	49.4	(142)
Salicylate	1500 mg	12	50	2	60	60.3±13.3	52.5±7.0*	12.9[A]	(143)
Salicylate	975 mg	10	10	2	<5	98.6±3.2	69.5±6.8†	29.5[A]	(144)
Salicylate	972 mg	8	20	3	<5	91.7±4.7	62.3±18.4*	32.1[A]	(140)
Salicylate	1000 mg	5	1.9	1	0	99.7	87.4†	12.3[A]	(21)
Salicylate	1000 mg	5	10	1	0	99.7	60.6†	39.2[A]	(21)
Salicylate	1000 mg SR	4	10	1	<5	89.1±7.7	63.2±7.0†	29.1[A]	(145)
Salicylate	1000 mg EC	4	10	1	<5	96.2±6.0	71.2±10.5†	26.0[A]	(145)
Salicylate	2925 mg EC	10	50	3, 4	240	100	43†	57[B]	(36)
Sotalol	160 mg	7	50	2	5	64.3±5.9[F,H]	0.5±0.3*	99.2	(146)
Sulphadoxine	1500 mg	10	2	4	5	2533.0±5.1[H,I]	1346.3±85.2*	46.8	(147)
Tetracycline	500 mg	6	50	2	5	100	3†	97.0[B]	(116)
	500 mg	6	50	2	30	100	38*	62.0[B]	(116)
Theophylline	10 mg/kg SR	5	1 g/kg	1	0	97±4	38±6†	60.8	(148)
Theophylline	500–600 mg	5	30	1	30	209.4±23.6	74.3±25.4*	64.5	(149)
Tilidine	44.2 mg	3	20	2	3	2.91±1.21	0.31±0.09†	89.3[C]	(150)
Tilidine	44.2 mg	3	20	2	25	2.91±1.21	1.35±0.53†	53.6[C]	(150)
Tolbutamide	500 mg	6	50	2	<5	714±53[H]	78±22*	89.1	(151)
Tolfenamic acid	400 mg	6	25	2	<5	18.6±2.3[H]	2.29±0.26*	87.7	(134)
Tolfenamic acid	400 mg	6	25	2	60	18.6±2.3[H]	7.02±2.08*	62.3	(134)
Tolfenamic acid	200 mg	6	2.5	2	<5	9.50±1.20[H]	0.33±0.06*	96.5	(138)
Trimethoprim	200 mg	6	2.5	2	<5	41.5±7.3[H]	3.8±0.9*	90.8	(129)
Trimethoprim	200 mg		10	2	<5	41.5±7.3[H]	1.0±0.2*	97.6	(129)
Trimethoprim	200 mg		25	2	<5	41.5±7.3[H]	Unmeasurable*	100.0	(129)

(*continued*)

Appendix 1. Continued

Drug (dose)	Dose	n=	Activated charcoal			Mean (±SD) bioavailability[c,d]		Per cent reduction[e]	Ref.
			Dose (g)	Form[a]	Delay[b] (min)	Control	Charcoal		
Trimethoprim	200 mg		50	2	<5	41.5±7.3[H]	Unmeasurable*	100.0	(129)
Trimethoprim	200 mg		10	3	<5	41.5±7.3[H]	Unmeasurable*	100.0	(129)
Valproate	300 mg	6	50	2	<5	609±71[H]	222±58*	63.5	(151)
Verapamil	80 mg	9	25	3	0	270±89[D]	3.9±4.0[D]	99	(30)
Verapamil	80 mg	9	25	3	120			98	(30)
Verapamil	240 mg	8	25	3	0	1132±515[D]	158±189[D]	86	(30)
Verapamil	240 mg	8	25	3	120	1132±515[D]	731±512[D]	35	(30)

Key to comments:

[a]1-activated charcoal 900–1500 mg/m^2; 2=activated charcoal 1600–2000 mg/m^2; 3=unknown charcoal; 4=with sorbitol; 5=with saline cathartic; 6=Medicoal®.

[b]Delay (min) in giving charcoal after drug administration.

[c]Area under the curve (mg·hr/mL) unless otherwise stated in comments.

[d] *$p<0.05$;† $p<0.01$;‡ $p<0.001$; otherwise, not significant.

A=% urinary excretion of dose; B=% of control; C=recovered in urine (mg); D=ng·hr/mL; E=µmol·hr/mL; F=mmol·hr/mL; G=mg·min/mL; H=data expressed as±SEM; I=not crossover design.

APPENDIX 2

A Technique For Administering Single-Dose Activated Charcoal

- Activated charcoal can be administered orally as a drink or through a nasogastric tube. If the patient is unconscious, a nasogastric tube with airway protection is mandatory.
- Activated charcoal products should be shaken vigorously prior to use to ensure adequate dispersion of the charcoal in the liquid and administration of the prescribed dose. The activated charcoal container should be rinsed thoroughly with water and the remaining contents should be administered to the patient.
- Cathartics, such as sorbitol, mannitol, magnesium citrate, and sodium and magnesium sulfate should never be administered to the poisoned patient, with or without activated charcoal.