ORIGINAL CONTRIBUTION
theophylline, activated charcoal, experimental;
theophylline, poisoning, experimental

Intravenous Theophylline Poisoning and Multiple-Dose Charcoal in an Animal Model

Large overdoses of IV theophylline (50 to 100 mg/kg) were administered to five canines on two separate occasions. On day one, with no charcoal administered, theophylline levels were serially obtained between ten minutes and 12 hours after infusion and the animals were recovered from anesthesia. Three days later the same dose of theophylline was administered, but then 50 g activated charcoal was placed through a nasogastric tube into the duodenum every hour for eight doses. In all five animals tested, activated charcoal significantly decreased the area under the serum concentration-time curve, decreased the half-life of elimination, and increased the clearance of theophylline. This effect on pharmacokinetics was not seen when the nasogastric tube was put into the stomach instead of the small bowel because the charcoal administered did not pass beyond the pylorus. In a separate experiment in which bile theophylline concentrations were measured, it was demonstrated that enhanced elimination was not from interruption of enterohepatic circulation of theophylline. This suggests that the demonstrated physiologic mechanism is that of gastrointestinal dialysis. [Kulig KW, Bar-Or D, Rumack BH: Intravenous theophylline poisoning and multiple-dose charcoal in an animal model. Ann Emerg Med August 1987;16:842-846.]

Kenneth W Kulig, MD, FACEP*†
David Bar-Or, MD†
Barry H Rumack, MD*
Denver, Colorado

From the Rocky Mountain Poison & Drug Center,* and the Department of Emergency Medicine,† Denver General Hospital, Denver, Colorado.

Received for publication July 30, 1986.
Revision received March 23, 1987.
Accepted for publication May 22, 1987.

Data presented at the American Association of Poison Control Centers/ American Association of Clinical Toxicology/American Board of Medical Toxicology/Canadian Association of Poison Control Centers Annual Scientific Meeting in Boston, Massachusetts, August 1983.

Dr Kulig was the recipient of a McNeil Fellowship in Clinical Toxicology at the time of this investigation.

Address for reprints: Kenneth W Kulig, MD, Rocky Mountain Poison & Drug Center, 645 Bannock Street, Denver, Colorado 80204-4507.

INTRODUCTION

Theophylline administered intravenously in therapeutic doses to human volunteers has a shortened half-life of elimination when activated charcoal is administered orally.[1-5] We attempted to discover to what extent activated charcoal can enhance the elimination of theophylline given intravenously in large overdose quantities to experimental animals. This particular experimental setting is important because 1) possible differences could exist in the kinetics of theophylline given in overdose instead of therapeutic quantities; 2) by giving the theophylline intravenously we could be certain that any alteration in kinetics from charcoal was not due to the adsorption of drug remaining in the gut, such as occurs after an ingestion; and 3) patients may certainly be iatrogenically overdosed with IV theophylline.[6]

METHODS

Our study was approved by the Animal Care and Use Committee of Denver General Hospital. Mongrel adult dogs weighing 14 to 25 kg were premedicated with 0.25 mg/kg acepromazine maleate IM, and then anesthetized with 23 mg/kg IV pentobarbital. Endotracheal intubation was performed and the animals were placed on mechanical ventilators. IV catheters were placed in the external jugular veins, and the animals were monitored continuously for arrhythmias. Pentobarbital was further administered IV as needed for proper and humane anesthesia, and the animals were extubated and allowed to wake up after the 12-hour level was obtained.

Each animal acted as its own control. In the first phase of the experiment aminophylline in doses of 50, 80, or 100 mg/kg was administered over exactly 20 minutes in 300 mL of normal saline. Theophylline levels then were obtained at ten, 20, and 30 minutes, and at one, two, four, five, eight, and 12 hours after infusion.

In the second phase of the experiment (three to four days later) all of the above procedures were carried out in the same manner. In addition, a midline

TABLE 1. *Pharmacokinetic parameters*

No.	Dose	AUC_{Cont}*	AUC_{AC}†	△ AUC	T ½$_{Cont}$(hr)	T ½$_{AC}$(hr)	△ T ½ (hr)	Cl_{Cont} (mL/min)	Cl_{AC} (mL/min)	△ Cl (mL/min)
1	50 mg/kg	350.93	229.64	↓35%	3.7	2.9	↓21%	31.48	55.30	↑75%
2	50 mg/kg	219.06	148.88	↓32%	3.6	2.2	↓39%	56.83	83.62	↑32%
3	80 mg/kg	455.64	355.51	↓22%	4.8	3.0	↓38%	42.16	54.11	↑28%
4	80 mg/kg	663.51	424.60	↓36%	5.5	3.3	↓40%	34.48	53.88	↑36%
5	100 mg/kg	650.53	344.59	↓47%	5.1	2.1	↓59%	36.96	69.78	↑89%

*Control, no charcoal administered.
†Same animals given 50 g of activated charcoal into duodenum every hour for eight doses.

abdominal incision approximately 8 cm in length was made under sterile conditions, and a 16-Fr nasogastric tube was placed into the small bowel through a 2-cm incision in the stomach wall by passing the tube manually through the pylorus. Meticulous hemostasis was carried out, and the nasogastric tube was inserted approximately 10 cm beyond the pylorus and secured with a purse-string suture. The wound was sutured and covered with a sterile dressing.

Aminophylline was given in the same doses to the same animals, but in addition, 45 to 50 g of activated charcoal (Insta-Char®, Kerr Chemical Co, Northville, Michigan) was administered in water through the nasogastric tube at the end of the infusion and at one, two, three, four, five, six, and seven hours after infusion (eight doses). Serum theophylline levels were obtained at the same intervals as in the first part of the experiment, but levels also were obtained prior to the infusion in the second part of the experiment to confirm that they had fallen to zero in the interim.

In a separate experiment, the same anesthetic and monitoring procedures were performed, but were followed by a midline laparotomy and cannulation of the gall bladder in two dogs. A size 8-Fr feeding tube was placed into the gall bladder and secured with a purse-string ligature. The common bile duct was ligated to ensure that all bile from the liver entered the cannula. In this experiment 80 mg/kg of aminophylline was infused over exactly 20 minutes, and serum levels were obtained at two, four, five, eight, and 12 hours after infusion. The entire volume of bile during this same period was collected in each animal, and the bile concentration of theophylline was measured.

TABLE 2. *Volume of distribution and elimination constants*

No.	Dose	Vd_{Cont}*(L/kg)	Vd_{AC}† (L/kg)	kel_{Cont}	kel_{AC}
1	50 mg/kg	.663	.802	.187	.236
2	50 mg/kg	.912	.919	.195	.318
3	80 mg/kg	1.061	.848	.144	.231
4	80 mg/kg	.836	.785	.126	.209
5	100 mg/kg	.983	.758	.136	.333

*Controls, no charcoal administered.
†Same animals given 50 g of activated charcoal into duodenum every hour for eight doses.

Areas under the curve (AUC) were calculated by the trapezoid rule. Other kinetic parameters were calculated by the following formulae:

$$Kel = \frac{\ln Cp_1/Cp_2}{\triangle t}$$

$$Vd = \frac{Dose}{AUC \times kel} \text{ L/kg}$$

$$T½ = \frac{0.693}{kel} \text{ hours}$$

$$Cl = \frac{Dose}{AUC} \text{ L/hr}$$

To determine the amount of theophylline excreted in bile over 12 hours the amount of theophylline remaining in the dogs (R_{12hr}) was calculated using the formula:

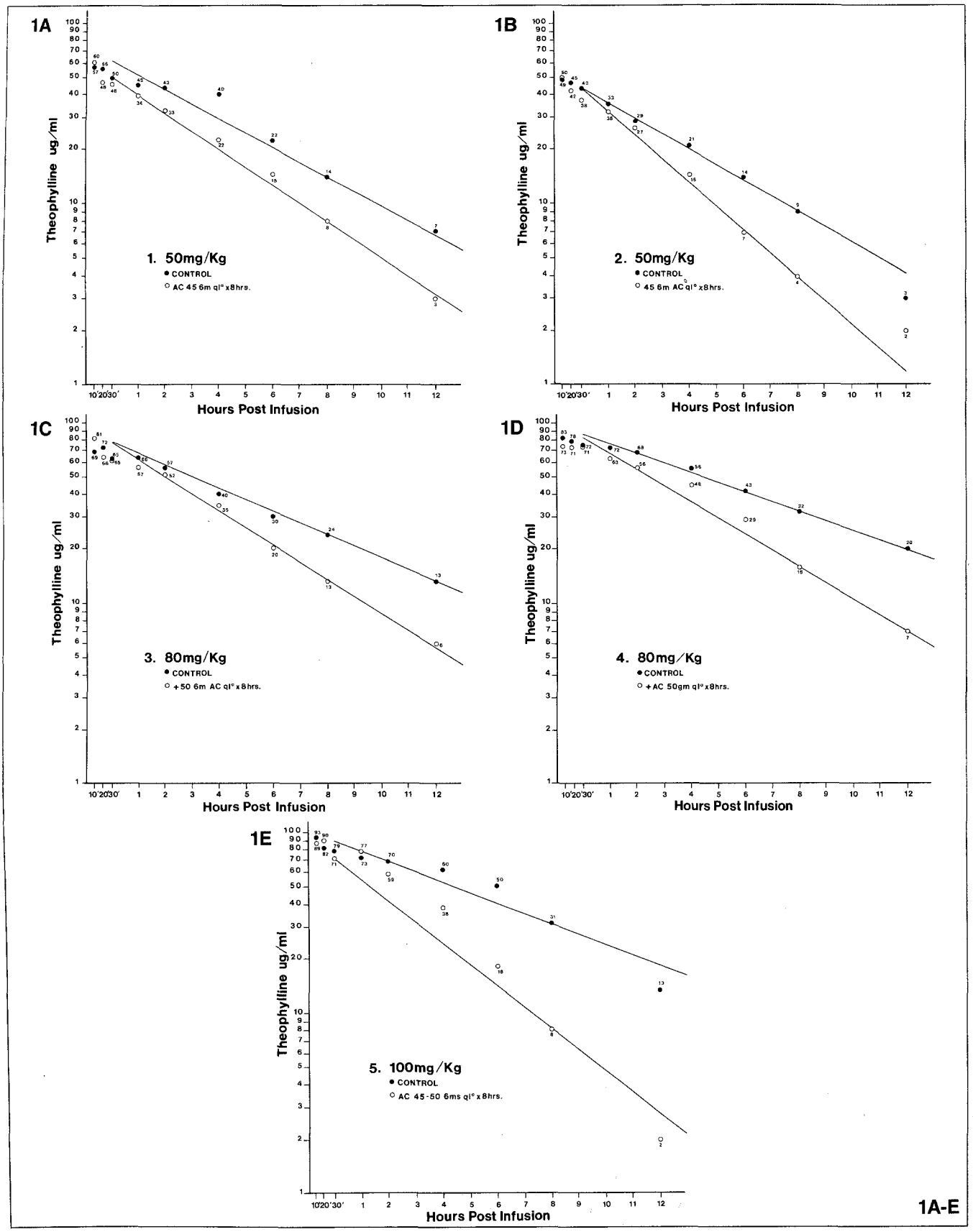
$$R_{12hr} = Cp_{12} \times Vd$$

where Cp_{12} is the plasma concentration at 12 hours after ingestion, and Vd is the volume of distribution calculated for each dog individually using the AUC. Subtracting R_{12hr} from the total dose of theophylline administered equals the total amount of theophylline excreted during the 12 hours after infusion.

The dose of aminophylline administered was multiplied by 0.87 to reflect the fact that aminophylline is 87% theophylline (dose-equivalent). The clearances calculated in L/hr were multiplied by 16.6 to convert them to units of mL/min.

Theophylline levels were done by High Performance Liquid Chromatography (Analytitox, Inc, Denver, Colorado). The extract consisted of a solid phase separation technique using 100 μL of sample and 40 μg/mL of 8-chlorophylline as internal standard. Caffeine was included in the standards to demonstrate its lack of interference. There was no detectable level of caffeine in any of the dogs (less than 2 μg/mL). The final extracts were dissolved in 0.25 mL of methanol and 10 μL of each was injected on the liquid chromatograph (Beckman HPCC, model 334; Beckman variable wavelength detector, model 165; Beckman Instruments, Inc, Scientific Instruments Division, Berkeley, California).

FIGURE 1A-1E. *Serial theophylline levels in five subjects with and without multiple-dose charcoal administration.*


1A
Theophylline ug/ml
1. 50mg/Kg
● CONTROL
○ AC 45 6m qI° x8hrs.
Hours Post Infusion
1B
Theophylline ug/ml
2. 50mg/Kg
● CONTROL
○ 45 6m AC qI° x8hrs.
Hours Post Infusion
1C
Theophylline ug/ml
3. 80mg/Kg
● CONTROL
○ +50 6m AC qI° x8hrs.
Hours Post Infusion
1D
Theophylline ug/ml
4. 80mg/Kg
● CONTROL
○ +AC 50gm qI° x8hrs.
Hours Post Infusion
1E
Theophylline ug/ml
5. 100mg/Kg
● CONTROL
○ AC 45-50 6ms qI° x8hrs.
Hours Post Infusion
1A-E

The column used was a 150 × 4.6-mm ultrasphere ODS; run at ambient temperature, 87.5% phosphate buffer, pH 3.0, 17.5% acetonitrile. The flow rate of the column was 1.5 mL/min.

RESULTS

During the initial trial of this experimental technique the nasogastric tube was inserted orally into the stomach in one dog. After eight hours no charcoal stool had appeared, despite the fact that a total of 450 g of charcoal had been given. Therefore a postmortem laparotomy was performed, and it was discovered that the entire amount of administered charcoal had remained in the stomach. We found that there was no effect on the elimination of theophylline in this case. Because it appeared that activated charcoal must move beyond the pylorus to increase theophylline elimination, all subsequent subjects had a nasogastric tube passed directly into the duodenum through a small laparotomy incision. Only the data obtained from these animals were analyzed.

In each case there was an enhancement of elimination by the activated charcoal (Figure). The cumulative data on means with standard deviations could not be analyzed statistically because three different doses of aminophylline (50, 80, or 100 mg/kg) were used. Variable dosing was done because as the experiment progressed, we learned that higher doses could be administered without causing convulsions or arrhythmias, and the dogs could be recovered from anesthesia safely and humanely. We therefore attempted to give the highest dose possible.

Pharmacokinetic parameters for each subject are detailed (Tables 1 and 2). In every case there was a decrease in AUC and half-life with a corresponding increase in clearance. There were slight variations in volume of distribution and elimination constants (Table 2), parameters one would expect to remain constant. These variations did not have a significant effect on the changes seen for AUC, half-life, and clearance.

In the separate experiment where bile concentrations were measured in bile collected over 12 hours from two separate animals (subjects A and B, Table 3), the percentage of bile elimination of theophylline was only 1.89% and 2.38%, respectively, of the total body elimination of theophylline during the same 12 hours.

TABLE 3. *Bile secretion of theophylline*

	Subject A	Subject B
Total bile volume	134 mL	68 mL
Bile theophylline concentration	76 μg/mL	82 μg/mL
Theophylline excreted in bile mg/12 hours	10.18 mg	5.58 mg
% excreted in bile	1.89%	2.38%

DISCUSSION

In vitro studies have shown that one gram of activated charcoal will bind almost 300 mg of theophylline, compared to a maximum of 133 mg of aspirin.[7] *In vivo* experiments in volunteers demonstrated that only 40% of an administered oral dose of theophylline (7.7 mg/kg) was absorbed into the blood when 30 g of activated charcoal was administered 30 minutes afterwards as a single dose.[8]

The effect of multipe-dose charcoal (MDC) on theophylline kinetics has been studied more for theophylline than for any other drug. The reasons for this include: the kinetics of theophylline are well known; it has a relatively small volume of distribution and short half-life, which makes it ideal for these types of studies; theophylline overdoses are relatively common; IV overdoses with theophylline do occur; and MDC therapy is relatively benign when compared to hemodialysis or hemoperfusion, which are often recommended in cases of theophylline poisoning.

Unfortunately, one of the earliest symptoms of theophylline toxicity is vomiting, which may make the administration of charcoal very difficult.[9] On the other hand, patients in coma from coingestants or from complications of theophylline toxicity (ie, convulsions, cardiac arrest) may have greatly delayed gastric emptying. As we have seen in this experiment, if the charcoal does not get through the pylorus it will not have an effect on theophylline elimination. The delayed gastric emptying that occurred in our study was probably the result of acepromazine pretreatment and pentobarbital anesthesia. Because of the strict requirements of the Surgical Research Laboratory at Denver General Hospital that all animal experimentation be performed in a proper and humane manner, there was no alternative to using these medications.

The scenarios in which MDC therapy has been examined in theophylline pharmacokinetic studies have included: therapeutic IV theophylline doses in healthy volunteers[1-5] and in patients with cirrhosis;[5] IV overdoses in experimental animals;[10,11] and in patients with either a deliberate[5,6,9,12,13] or iatrogenic[5,6,9,14] overdose. MDC therapy has been used successfully for theophylline toxicity in a pregnant patient,[15] a premature newborn,[16] and an infant.[17]

It is clear from the data obtained from the above studies, plus our own that MDC therapy enhances the elimination of theophylline from the blood. The presumed mechanism has been termed gastrointestinal dialysis,[18] whereby drug secreted from the blood into the gut lumen (actively or passively) cannot be reabsorbed because it becomes bound to charcoal.

Our study demonstrated that 98% of the theophylline elimination occurring in the first 12 hours after infusion did not involve bile elimination. Therefore, any interruption of enterohepatic circulation of theophylline in this model did not account for the marked changes in kinetics seen. The time course and doses of pentobarbital for anesthesia could not have caused a change in the kinetics of theophylline by enzyme induction. This study was not conducted in a randomized crossover design because of the subsequent necessity and expense of ensuring that all of the charcoal administered in a Phase I trial would have cleared from the GI tract by the time of Phase II. Because a total of 450 g of charcoal was administered, this may have taken weeks.

The optimum dose of charcoal and

time interval between doses is unknown. This may depend on other drug(s) ingested and the patient's clinical condition. Park et al have shown in volunteers that smaller, more frequent doses of charcoal may be as effective as larger, less frequent doses.[2] Because this group has also shown an advantage in using a larger surface-area charcoal,[3] they are currently recommending 30 g of super-activated charcoal every two to six hours until the patient is no longer symptomatic or until plasma drug concentrations are well below the toxic range.[19]

CONCLUSION

Our study demonstrated that multiple-dose charcoal can enhance the elimination of theophylline given as a massive IV overdose to experimental animals. In addition, the bile elimination of theophylline was shown to be insignificant, providing further evidence that the theory of gastrointestinal dialysis instead of interruption of enterohepatic circulation was operative in this model.

The authors thank the Frank W Kerr Chemical Company and Analytitox, Inc for their generous financial support of this project, as well as Charles van Way, MD, Sharon O'Reilly, RN, and Lisa Wolfe for their invaluable assistance.

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