Randomized Study of the Treatment of Phenobarbital Overdose With Repeated Doses of Activated Charcoal

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• **We performed a prospective randomized study of the effectiveness of repeated oral doses of activated charcoal in the treatment of phenobarbital overdose. Ten comatose patients who required intubation and mechanical ventilation completed the protocol. Five patients received repeated doses of activated charcoal and sorbitol. Five other patients who received a single dose of charcoal and cathartic served as control subjects. The serum half-life of phenobarbital (mean ± SD, 36 ± 13 hours) during repeated administration of charcoal and sorbitol was significantly shorter than that after charcoal administration was discontinued (93 ± 7 hours) and shorter than the half-life in the single-dose group (93 ± 52 hours). The length of time that patients in each group required mechanical ventilation, 39 ± 24 hours (single-dose group) and 48 ± 8 hours (repeated-dose group), did not differ significantly, nor did the time spent in the hospital. Although administration of repeated doses of activated charcoal to patients with phenobarbital overdose significantly increased the elimination of phenobarbital, it had no clear effects on the patients' clinical course.**

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USE of charcoal as a medicinal agent has a long history.[1] Hippocrates and Pliny used wood charcoal to treat a number of diseases. The first studies of the efficacy of charcoal as an antidote were performed in France in the 1800s. Public demonstrations of its effectiveness were given by a chemist who swallowed 5 g of arsenic trioxide mixed with charcoal and by a pharmacist who swallowed five times the lethal dose of strychnine along with 15 g of charcoal. Both men survived.[1]

See also p 3130.

Recently, interest has focused on the use of activated charcoal to interrupt the enterohepatic and enteroenteric circulation of drugs and thus enhance their elimination.[2-7] Neuvonen and Elonen[3] demonstrated, in normal volunteers, that repeated oral doses of activated charcoal increased the rate of elimination of phenobarbital, carbamazepine, and phenylbutazone, which had been administered orally ten hours before charcoal therapy was begun. To prove that the charcoal was not merely binding unabsorbed phenobarbital, Berg et al[6] administered phenobarbital intravenously (IV) to normal subjects; repeated oral doses of activated charcoal increased elimination significantly. Goldberg and Berlinger[7] treated two patients after phenobarbital overdose with repeated doses of charcoal and cathartic administered through a nasogastric tube. The patients were comatose for shorter times than historical controls treated without charcoal. These preliminary reports have encouraged many physicians to administer repeated doses of activated charcoal orally to patients with a variety of drug overdoses.

The benefit and safety of any new treatment should be established before it is adopted widely. More than 90% of patients who have taken an overdose of barbiturates survive if they reach the hospital, because intensive supportive care is highly effective treatment.[8,9] If activated charcoal shortens the serum elimination half-life of phenobarbital and the coma time of patients who have taken an overdose, it would be a logical

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addition to the usual management of drug overdose. Potential complications, however, of administering repeated doses of activated charcoal orally include pulmonary aspiration[10] and constipation.[11] If a cathartic is used, fluid and electrolyte imbalance may be produced by the osmotic diarrhea.[12] We therefore performed a randomized, prospective study to evaluate the therapeutic effect and safety of administering oral doses of activated charcoal and sorbitol to patients after phenobarbital overdose.

PATIENTS AND METHODS

Patient Selection

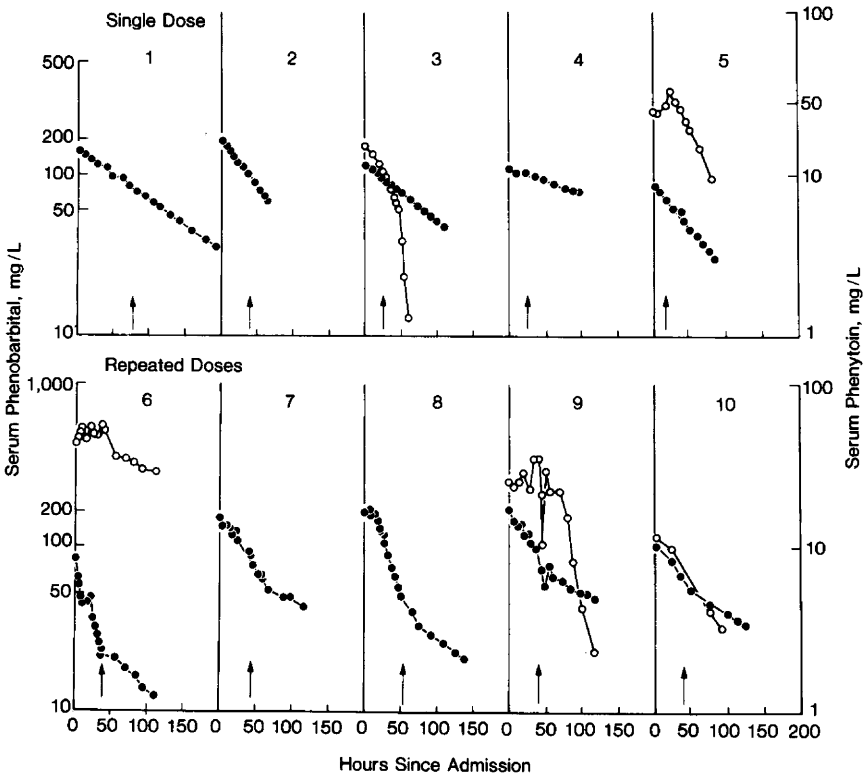
Patients were admitted consecutively to the study (which was approved by the University of California, San Francisco, Committee on Human Experimentation) as they entered the San Francisco General Hospital if they fulfilled the following criteria: (1) relatives, friends, or paramedics gave a history of possible overdose with phenobarbital and/or the patient had a serum phenobarbital concentration above 60 mg/L on admission and (2) the patient was sufficiently obtunded to require intubation and mechanical ventilation.

Study Design

All patients who met the criteria underwent gastric lavage, which was performed through a 24-gauge Harris tube with 2 L of normal saline. Then, 50 g of activated charcoal in 250 mL of magnesium citrate was administered through the tube. Thereafter, patients were randomly assigned, by opening sequentially numbered envelopes, to the group that would receive no further charcoal-cathartic suspension (single-dose group) or to the group that would receive repeated doses of charcoal-cathartic (repeated-dose group). Blood specimens were screened for the following compounds: alcohol, methanol, acetone, isopropanol, primidone, methyprylon, butabarbital, butalbital, ethchlorvynol, phenytoin, amobarbital, glutethimide, secobarbital, methaqualone, acetaminophen, salicylate, and theophylline; urine specimens were screened for the following compounds: oxazepam, diazepam, nordiazepam, chlordiazepoxide, phencyclidine, amphetamine, methamphetamine, cocaine, benzoylecgonine, ecgonine methylester, propoxyphene, morphine, codeine, and phenothiazines.

Patients in the repeated-dose group received 17 g of activated charcoal in 70 mL of 70% sorbitol through the nasogastric tube every four hours until extubation was effected. Immediately before each dose, the stomach was emptied. Any residue from the previous charcoal-sorbitol dose was removed by suction, discarded, and the amount recorded.

All patients in both groups received supportive care in the intensive care unit, including mechanical ventilation and administration of fluids and pressor agents, and antibiotics when necessary. Neurologic status was assessed by examining verbal responses, eye opening, pupillary reaction, spontaneous eye movements, oculocephalic responses, corneal reflexes, respiratory pattern, motor responses, deep tendon reflexes, and skeletal muscle tone.[13] The individual scores assigned to the type of response within each of these groups



Serum phenobarbital (solid circles) and phenytoin (open circles) concentrations in ten patients. Five patients (top) received single dose of activated charcoal, 50 g, and magnesium citrate at time 0 (admission to hospital). Five patients (bottom) received single dose of charcoal and magnesium citrate on admission and then repeated doses of charcoal, 17 g, and 70% sorbitol, 70 mL, every four hours until extubation. Arrow indicates time at which patients met stipulated criteria for withdrawal of mechanical ventilation.

Table 1.—Clinical Features on Admission in Ten Patients With Phenobarbital Overdose

	Mean ± SD (Range)	
	Single-Dose Group	Repeated-Dose Group
Age, yr	27 ± 9 (20-43)	30 ± 11 (25-48)
Weight, kg	66 ± 5 (59-73)	63 ± 8 (52-74)
Mean arterial pressure, mm Hg	85 ± 19 (60-108)	76 ± 32 (26-105)
Heart rate, beats/min	95 ± 10 (84-110)	90 ± 16 (64-100)
Rectal temperature, °C	36.9 ± 1.5 (35.9-39.4)	36.5 ± 0.4 (36.1-36.9)
Arterial blood gases		
pH	7.4 ± 0.1 (7.3-7.4)	7.4 ± 0.1 (7.3-7.4)
Po_2, mm Hg	88 ± 39 (54-150)	84 ± 19 (74-118)
Pco_2, mm Hg	46 ± 6 (42-54)	42 ± 10 (30-53)
HCO_3, mEq/L	25 ± 4 (21-30)	22 ± 3 (18-25)
Fraction of inspired oxygen	0.2 (0.2)	0.2 ± 0.1 (0.2-0.4)

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Table 2.—Clinical Study and Pharmacokinetic Data

Patient No./Sex	Admission Data: Dose of Phenobarbital, g	Time Before Admission Dose Ingested, hr	Other Drugs Taken	Coma Score	Chest Roentgenographic Findings	Blood Alcohol, mg/dL	Serum Phenytoin, mg/L	Serum Phenobarbital, mg/L
Single-dose group								
1/M	3	Unknown	...	19	Normal	...	...	140
2/M	3.6	20	...	18	Left lung infiltrate	...	...	164
3/M	6	Unknown	Phenytoin	25	Normal	...	15	112
4/M	Unknown	Unknown	Alcohol	11	Normal	21	...	103
5/M	1.8	0.5	Phenytoin	30	Normal	...	25	86
Mean ± SD	...	...	...	21 ± 7	...	...	...	121 ± 31
Repeated-dose group								
6/F	10	0.5	Phenytoin	20	Right lung infiltrate	...	43	84
7/M	Unknown	Unknown	...	21	Normal	...	...	150
8/F	6	4	Alcohol	17	Normal	60	...	159
9/M	Unknown	Unknown	Phenytoin, alcohol	15	Right lung infiltrate	87	25	164
10/M	Unknown	24	Phenytoin	25	Normal	...	12	105
Mean ± SD	...	...	...	20 ± 4	...	...	...	132 ± 36
P	...	...	...	...	...	...	...	> .05

were added together. The lowest score a patient could obtain was 10 and the highest was 39. A score of 10 indicated that the patient was completely unresponsive, whereas an alert, conscious patient was given a score of 39. The following outcomes were recorded: (1) length of time that mechanical ventilation was required, (2) length of time that the patient was intubated, (3) length of hospital stay, (4) cardiopulmonary complications, and (5) other complications.

Patients had to meet specific criteria before mechanical ventilation could be discontinued. Once these were met, patients were weaned as follows: a T-piece trial was performed if the patient (1) was conscious, (2) was capable of maximal inspiratory negative pressure of more than 20 cm H_2O, (3) had a vital capacity of more than 10 mL/kg, and (4) had a Pa_{O_2} of more than 60 mm Hg with an inspired oxygen concentration of 21%. These criteria were assessed at least twice daily. Once a patient had met the criteria for a T-piece trial, the staff usually waited until 8 AM the following morning so that extubation could be performed under optimal conditions. The T-piece was then connected for 30 minutes. If the arterial blood gases remained adequate, extubation was performed. The length of time until the patient successfully met the criteria for the T-piece trial was recorded as the length of time that the patient required mechanical ventilation.

Collection of Biologic Samples

Every four hours until extubation was performed and every eight hours thereafter for at least 64 hours, 5 mL of blood was obtained for determination of drug concentrations. The serum was separated and frozen at −80 °C until analysis. All urine was collected at 12-hour intervals until extubation and thereafter at 24-hour intervals. Phenobarbital and phenytoin concentrations were measured by high-performance liquid chromatography.[14]

Pharmacokinetic Analysis

The phenobarbital half-lives were determined by regression analysis of the linear serum phenobarbital concentration-time curves. The one-compartment model was used for the pharmacokinetic analysis. Renal clearance was calculated by dividing the amount of phenobarbital recovered in the urine by the area under the serum concentration-time curve during the same time interval.

Statistical Analysis

Differences within and between groups were analyzed by the Wilcoxon matched-pairs signed-ranks test and the Mann-Whitney *U* test, respectively.[15]

RESULTS

Fourteen patients with phenobarbital overdose were entered into the study during a 15-month period. Ten patients completed the protocol. Pertinent clinical features on admission are presented in Table 1. No differences between the two groups were statistically significant. Clinical study and pharmacokinetic data are presented in Table 2. In most cases, the dose of phenobarbital and the time of ingestion were not known. All ten patients had a history of grand mal epilepsy for which they had taken anticonvulsants for at least five years. Two patients in the single-dose group and three in the repeated-dose group had measurable serum concentrations of phenytoin on admission to the hospital. One patient in the single-dose group and two in the repeated-dose group had alcohol detected in the blood at the time of admission. No other compounds were detected. One patient in the single-dose group and two in the repeated-dose group had evidence of aspiration pneumonia on the chest roentgenograms obtained at the time of admission. Drugs used in the intensive care unit were penicillin G sodium for aspiration pneumonia and antacids. None of the patients required vasopressor agents. No charcoal-sorbitol residue was left in the stomach four hours after each dose.

Patients in the single-dose group required mechanical ventilation for 39 ± 24 hours; those in the repeated-dose group required it for 48 ± 8 hours ($P > .05$). Four of the five patients in the single-dose group met the criteria for extubation sooner than any of those in the repeated-dose group. Both groups spent a similar amount of time in the hospital (6 ± 2 *v* 6 ± 1 days).

By the second day of treatment, all five patients in the repeated-dose group had diarrhea, excreting 4 or 5 L of fluid each day. Fluid and electrolyte losses were replaced; this did not influence the length of hospitaliza-

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in Ten Patients With Phenobarbital Overdose

Drugs Used in Hospital	Clinical Course: Time Before Criteria Met for Extubation, hr	Clinical Course: Time Intubated, hr	Clinical Course: Time in Hospital, Days	Clinical Course: Serum Phenobarbital (When Ready for Extubation), mg/L	Pharmacokinetic Data: Serum Phenobarbital Half-Life, hr: During Intubation	Pharmacokinetic Data: Serum Phenobarbital Half-Life, hr: After Extubation	Pharmacokinetic Data: Renal Clearance of Phenobarbital, mL/min: During Intubation	Pharmacokinetic Data: Renal Clearance of Phenobarbital, mL/min: After Extubation
Antacids	80	96	8	70	96	96	1.4	3.5
Penicillin	36	36	9	85	52	52	3.0	1.5
...	36	45	6	91	70	70	0.4	0.6
...	24	24	4	100	178	178	1.1	1.7
...	18	30	5	69	68	68	0.8	1.3
...	39±24	46±29	6±2	83±13	93±52	93±52	1.3±1.0	1.7±1.1
Penicillin	40	44	6	22	26	98	2.5	1.7
...	60	63	6	60	40	96	0.4	0.3
...	49	53	6	48	22	82	0.4	0.3
Penicillin	44	48	5	59	41	99	1.6	2.0
...	48	48	6	56	53	90	D*	D*
...	48±8	51±7	6±1	49±16	36±13	93±7	1.6±0.9	1.2±0.8
...	>.05	>.05	>.05	<.01	<.01	>.05	>.05	>.05

*D indicates sample discarded.

tion. No subjects aspirated the charcoal-sorbitol slurry.

The serum concentration-time profiles of phenobarbital and phenytoin are shown in the Figure. The mean serum phenobarbital concentration on admission was 121±31 mg/L (mean±SD) in the single-dose group and 132±36 mg/L in the repeated-dose group (Table 1) ($P>.05$). At the time that the criteria for extubation were met, the serum phenobarbital concentration in the single-dose group was 83±13 mg/L, which was significantly higher ($P<.01$) than in the repeated-dose group (49±16 mg/L).

The serum phenobarbital half-life in the patients in the single-dose group was 93±52 hours. In the repeated-dose group during the period of charcoal-sorbitol dosing, the half-life of phenobarbital was 36±13 hours. After extubation and cessation of charcoal-sorbitol, the half-life was 93±7 hours. The difference between half-lives before and after extubation was significant ($P<.025$). The renal clearances of phenobarbital were similar in the single-dose and repeated-dose groups both during and after charcoal administration (Table 1). Serum concentrations of phenytoin remained constant or increased during the repeated administration of charcoal-sorbitol.

Two patients in the single-dose group were withdrawn from the study. One was a 46-year-old woman who had a serum phenobarbital concentration of 70 mg/L at the time of admission to the hospital. It increased to 117 mg/L and the mean arterial pressure decreased to 50 mm Hg within 48 hours despite administration of large volumes of IV fluids and dopamine hydrochloride. The patient was hypothermic and had myoglobinuria and the adult respiratory distress syndrome. Because of continuing deterioration of clinical status, hemoperfusion was carried out.[16] This rapidly lowered serum phenobarbital concentrations. The patient recovered. The second patient was a 43-year-old woman who had a serum phenobarbital concentration of 184 mg/L at the time of admission. Six hours later, mean arterial pressure was 55 mm Hg and oliguria had developed despite administration of fluids and increasing amounts of dopamine. Hemoperfusion was performed and the patient recovered completely.

Two patients in the repeated-dose group were also withdrawn from the study. One was a 23-year-old man who had been unconscious for four days. He was hypothermic (temperature, 33.3 °C) and hypotensive on admission to the hospital. Twenty-four hours after admission, severe abdominal distention developed because of ischemic bowel; the necrotic tissue was resected, and the patient recovered completely. The second patient was a 50-year-old woman found unconscious at home. She was hypotensive (systolic BP, 80 mm Hg), hypothermic (rectal temperature, 33.3 °C), and in a deep coma. She became unresponsive to administered fluids and increasing amounts of dopamine and norepinephrine. Pulmonary edema and intractable metabolic acidosis developed. The patient had no bowel sounds, and the abdomen became increasingly distended and tense. Sixteen hours after admission, hemoperfusion was performed. During hemoperfusion, the blood pressure increased, the requirement for pressors decreased, and bowel sounds returned. The patient recovered without further complications.

COMMENT

Activated charcoal is the most effective single agent used to manage acute ingestions of toxins. Given early and in sufficient quantity, it retards or prevents the absorption of many drugs and chemicals.[1] Given in multiple doses to normal subjects, it has been shown to accelerate the removal of several drugs, including phenobarbital, carbamazepine, phenylbutazone,[2] theophylline,[17] and nadolol.[18] In patients who have taken an overdose, it has accelerated the removal of digitoxin,[4] phenobarbital,[7] dapsone,[19] and methotrexate.[20]

Sorbitol has been used with activated charcoal to decrease intestinal transit time. Investigations in rats showed that administration of sorbi-

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tol alone may decrease the area under the plasma concentration-time curve measured after ingestion of single doses of aspirin, chloroquine, chlorpheniramine, and pentobarbital.[21] Furthermore, a charcoal-70% sorbitol mixture reduced the area under the drug concentration-time curve of these four drugs more than the administration of either charcoal or sorbitol alone.[21]

We showed in five patients after phenobarbital overdose that the elimination half-life of phenobarbital decreased significantly during the administration of repeated oral doses of activated charcoal and sorbitol. Lack of change in serum phenytoin concentrations during the administration of the repeated doses was surprising, but could be explained by the extensive plasma protein binding of the drug, which would make only the small unbound fraction of the drug available for removal,[22] or by continued absorption of phenytoin.

Whether the use of repeated doses of activated charcoal influenced the course of the overdosed patients is important clinically. In this group of patients with moderately severe phenobarbital overdose, administration of repeated oral doses of activated charcoal and sorbitol did not appear to influence any measure of morbidity of the overdose. Both experimental and control groups were of similar age and weight and had comparable serum phenobarbital concentrations and depth of coma on admission. The outcome in all our patients was favorable. Both groups of patients spent a similar number of days in the hospital. The group that received only a single dose of charcoal and cathartic satisfied criteria for extubation with higher serum phenobarbital concentrations than the repeated-dose group. More tolerance to phenobarbital may have developed in the patients in this group than in those in the repeated-dose group. Alternatively, the enhanced removal of phenobarbital from the blood by charcoal may not have been paralleled by as rapid a decrease in brain concentrations of phenobarbital. The latter hypothesis, however, is not supported by the rapid awakening of patients from phenobarbital overdose observed during hemoperfusion.[16]

Statistical power analysis before the study began, using the reduction in phenobarbital half-life achieved by Neuvonen and Elonen[3] by repeated doses of charcoal as the effect size (α=.05, β=.8), indicated that seven subjects would be needed in each study group.[23] The study was terminated after five patients had completed each treatment when the annual review of data, required by the Committee on Human Experimentation, demonstrated the achievement of significant reduction in phenobarbital half-life but no difference in coma time or length of intubation. Because each of the mean values for these two measurements were slightly longer in the repeated-dose group than in the single-dose group, studying a larger sample size was not considered necessary.

On the basis of this small randomized trial, we conclude that administration of repeated doses of activated charcoal and sorbitol significantly hastens the elimination of phenobarbital. The favorable effect of repeated doses of charcoal on phenobarbital kinetics, however, does not appear to alter clinical outcome.

The attending physicians, house staff, and nursing staff at San Francisco General Hospital Medical Center, those in the respiratory intensive care unit in particular, assisted with this study.

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