Review

Repetitive Doses of Activated Charcoal in the Treatment of Poisoning

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Activated charcoal has found a renewed role in the management of overdosed patients. Routinely administered to reduce the gastrointestinal (GI) absorption of many drugs, growing evidence indicates that repeated doses of charcoal also may enhance drug elimination. Some drugs are excreted into the bile or gastric fluids (phencyclidine, digoxin) and are reabsorbed. Other drugs (theophylline, phenobarbital) can diffuse from the plasma into the lumen of the GI tract. Activated charcoal is administered at regular intervals to sequester these toxins in the GI tract, eventually causing their excretion in feces. This article reviews the evidence for the safety and efficacy of repetitive charcoal therapy. While supportive management remains the mainstay of therapy in poisoned patients, activated charcoal is inexpensive, effective, simple to administer, and may obviate the need for more invasive methods of toxin removal. (Am J Emerg Med 1987;5:305–310)

The problem of poisoning, accidental or intentional, is an everyday occurrence in most emergency departments. Unfortunately, most toxic agents lack specific antidotes. The mainstay of emergency therapy is to provide supportive care and limit further absorption of the toxic substance.[1] Immediate treatment includes oral sorbents, cathartics, emesis or gastric lavage, maintaining adequate ventilation and controlling fluid balance.[2]

Active methods of toxin removal such as dialysis (peritoneal or hemodialytic), column hemoperfusion (charcoal or resin), and exchange transfusion are recommended for certain severe intoxications. These methods may prevent or decrease many toxic effects and thereby shorten the duration of supportive care.[3] However, they are also invasive and associated with a number of complications, and they may require complicated and expensive equipment. Because of these factors, such techniques are used only in near-lethal intoxications, frequently after a delay of many hours following the patient's arrival in the emergency department.[1] A major focus in toxicologic research has been the clinical utility of repeated doses of activated charcoal in drug elimination.[4] Administered to reduce the gastrointestinal (GI) absorption of many drugs, recent evidence indicates that charcoal increases the clearance of drugs that already have been absorbed and are in the systemic circulation. Theoretically, activated charcoal can enhance the elimination of drugs secreted into the GI tract or enterohepatic circulation. The purpose of this study was to review the evidence for the safety and efficacy of this "gastrointestinal dialysis"[5] in toxicology.

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PHYSIOCHEMICAL CHARACTERISTICS

The medicinal uses of charcoal have been recognized for centuries. Hippocrates and Pliny used wood charcoal to treat a number of diseases.[6] The first studies of charcoal as an antidote were performed in France in the nineteenth century.[6] During the following hundred years several studies on activated charcoal were published, but its use as an antidote was not accepted until the mid-1970s.[7]

Activated charcoal is a tasteless, colorless, insoluble black powder produced by the destructive distillation of various organic materials, usually wood pulp.[8] The adsorptive capacity of charcoal is increased, or "activated," by treatment with steam and strong acids.[7,8] The activation process markedly increases the surface area of charcoal by creating a fine network of pores.[8] Recently, a new form of superactivated charcoal (Super-Char®) has become available. This modified charcoal may have two to three times greater adsorptive capacity per gram of charcoal because of its increased surface area (2,500 to 3,500 m^2/g).[9]

Activated charcoal has the ability to bind a wide variety of toxins to the surfaces of the unabsorbable charcoal particles.[7] This prevents the absorption of various drugs and toxins from the GI tract and, in some cases, increases their rate of elimination. In 1963, Holt and Holz stated that "of the emergency measures it is our belief that charcoal is probably the most effective single measure because of its broad spectrum of activity and its exceedingly rapid inac-

TABLE 1. Compounds Poorly Adsorbed by Activated Charcoal*[11,12,13]

Alcohols (ethanol, methanol)
Aliphatic hydrocarbons (gasoline naphtha, kerosene)
Alkali
Boric acid
Caustic acids (sodium hydroxide)
Cyanide
Heavy metals (iron, lead, mercury)
Lithium
Mineral acids
N-methylcarbamate
Pesticides (malathion, DDT)
Drugs insoluble in aqueous solutions

*Based on in vitro studies; in vivo binding of small amounts may affect clinical course in some patients (e.g., cyanide).

tivation of the poison."[10] Its administration is indicated in almost all serious oral overdoses except caustic agents, some heavy metals, and aliphatic hydrocarbons[11] (Table 1).

ADMINISTRATION OF ACTIVATED CHARCOAL (TABLE 2)

In light of the experimental and clinical data and extensive experience in Europe, physicians are beginning to recommend activated charcoal as a first-line treatment for most poisonings.[12] Syrup of ipecac and gastric lavage generally are not of benefit for the initial treatment of drug overdose unless lavage is performed within one hour of ingestion.[14] Activated charcoal therapy seems to carry less risks of serious complications than gastric lavage, and its efficacy is comparable.[2,7,13]

TABLE 2. Administration of Activated Charcoal*

Initial dose: 1 g/kg body weight (adults and children)
Repetitive doses: 0.5 g/kg body weight every four hours (adults and children)
Procedure:
1. Suspend charcoal in water, 70% sorbitol, or saline cathartic until a soup-like consistency is obtained.
2. The slurry may be drunk or passed through a lavage tube.
3. If the patient vomits the dose, it may be repeated (protect airway).
4. Continue dosing every four hours until the patient is stable and serum concentrations are normal (alternate sorbitol and aqueous suspensions).
5. Concurrent therapy (i.e., diuresis, alkalinization of urine, and dialysis) may be used as indicated.
6. Monitor fluid and electrolyte balance, gastrointestinal motility during therapy.

Contraindications:
1. Charcoal will not absorb caustic agents, some heavy metals, or aliphatic hydrocarbons.
2. Adynamic ileus or intestinal obstruction.
3. When specific antidotes (such as N-acetylcysteine or Mucomyst) are used concurrently with charcoal therapy, their dosage may need to be increased.

*Flomenbaum NE, Goldfrank LR, Kulberg AG, et al: General management of the poisoned or overdosed patient. *In* Goldfrank LR, Flomenbaum NE, Lewin NA (eds): Goldfrank's Toxicologic Emergencies. Norwalk, Connecticut, Appleton-Century-Crofts, 1986, pp 5–27.

In vivo and in vitro studies[15–17] show that the optimal binding capacity for most drugs is achieved when activated charcoal is administered in a dose that is 10 times the amount of ingested drug. However, in many intoxications the amount of drug taken is unknown. In practice, an *initial* dose of 1 g/kg (50 to 100 g in adults) is recommended.[11] Dosage regimens for repetitive charcoal therapy have been arbitrary and based on convenience.[17] However, approximately 0.5 g/kg charcoal (20 to 60 g) every four hours has been recommended for overdosed patients.[5,7,18] One study found little difference between the effects of the same total dose of charcoal every four hours versus every hour on the half-life of theophylline.[18] The conventional charcoal slurry is made by adding water or cathartics to activated charcoal until a soup-like consistency is obtained; it then may be drunk or passed via a lavage tube.

Activated charcoal and the adsorbed toxic substance form a reversible bond. As such, significant desorption from charcoal and subsequent systemic absorption of a drug is possible if inadequate amounts of charcoal are used.[7] GI contents, such as food, alcohol, and bile, reduce drug adsorption when tested in vitro.[19] The pH level may also influence the efficacy of activated charcoal. Weak acids and bases are better adsorbed when in their nonionized form.[7] For example, the binding capacity of activated charcoal for salicylate is approximately three times as great in an acid solution than at pH 7.4.[20] Such drugs may partially desorb with changing pH levels during transit through the GI tract.[20] The effects of GI contents and pH may be minimized by administering sufficient charcoal (1 g/kg body weight) to provide excess binding capacity.

Attempts to improve the palatability and patient acceptance of activated charcoal by adding flavorings, jams, and ice cream without impairing adsorptivity have been unsuccessful.[21,22] The use of a poorly absorbed sugar, 70% sorbitol, has improved patient compliance and may actually enhance the antidotal effect of charcoal.[23] This preparation is recommended because of its greater palatability, long shelf-life, and cathartic properties.[28]

PHARMACOKINETICS

Although a complete discussion of the pharmacokinetics of drug overdose is beyond the scope of this review, a brief summary of the kinetics of charcoal adsorption is important so that the rationale for its use in various intoxications may be understood. Maximum prevention of drug absorption

occurs when the charcoal suspension is given as soon as possible after ingestion.[23] However, following an acute overdose, a toxin's absorption may be prolonged up to 24 hours.[11] This may be due to the drug's limited solubility (phenytoin), anticholinergic properties (tricyclics), or decreased gastric emptying (methylsalicylate).[21] Therefore, late administration of charcoal may be able to "catch up" and prevent further absorption of toxin. Repetitive or pulse dosing of activated charcoal may further decrease drug absorption if the drug undergoes enterogastric or enterohepatic recirculation (Fig. 1).[21]

Several drugs are secreted unchanged or as active metabolites into the GI tract either in bile (digoxin),[24] gastric fluid (phencyclidine),[25] or other GI secretions and then are reabsorbed.[7] For example, drugs secreted in the form of water-soluble glucuronide conjugates (morphine) may be hydrolyzed by intestinal bacteria, resulting in a more lipid-soluble metabolite that is readily absorbed.[26] Anion-exchange resins,[27] fiber laxatives,[28] and antibiotics to eradicate intestinal flora,[29] have been recommended to interrupt this enterohepatic cycle. Their effect, however, is weak and may be influenced by many factors.[28,30] Activated charcoal, administered at regular intervals, appears to be a safe and effective method of sequestering toxins in the GI tract and eventually causing their excretion in the feces.[5] Insufficient information exists on the active secretion of many drugs and toxic chemicals to compare the contribution of this process on drug clearance to that of passive diffusion.

Activated charcoal not only adsorbs drugs present in the lumen of the GI tract, but attracts certain drugs from the plasma into the small intestine. When repetative doses of charcoal were administered orally to patients receiving intravenous phenobarbital, the rate of elimination was doubled and the half-life markedly reduced.[31] Because there is no appreciable enterohepatic circulation of phenobarbital, the drug was thought to diffuse from the circulation into the intestinal lumen.[31] This passive diffusion is facilitated by the large surface area of the small intestine, and driven by the elimination of phenobarbital from the GI fluids by charcoal.[31]

Not every drug will diffuse across the gut wall at a rate sufficient to make charcoal pulsing effective. The removal rate of a toxin depends on many factors, including volume of distribution, amount of protein binding, half-life, and the lipid solubility.[5] To maintain the concentration gradient, it is necessary to administer multiple doses of activated charcoal to replace that excreted in feces. Free drug or poison concentrations in the GI fluids should be essentially zero as long as the gut is full of charcoal and the adsorptive capacity of the charcoal is not exceeded. The effectiveness of charcoal may be reduced in patients with impaired gut motility (i.e., anticholinergic toxins, narcotics) or with decreased blood perfusion of the small intestine from shock.[5]

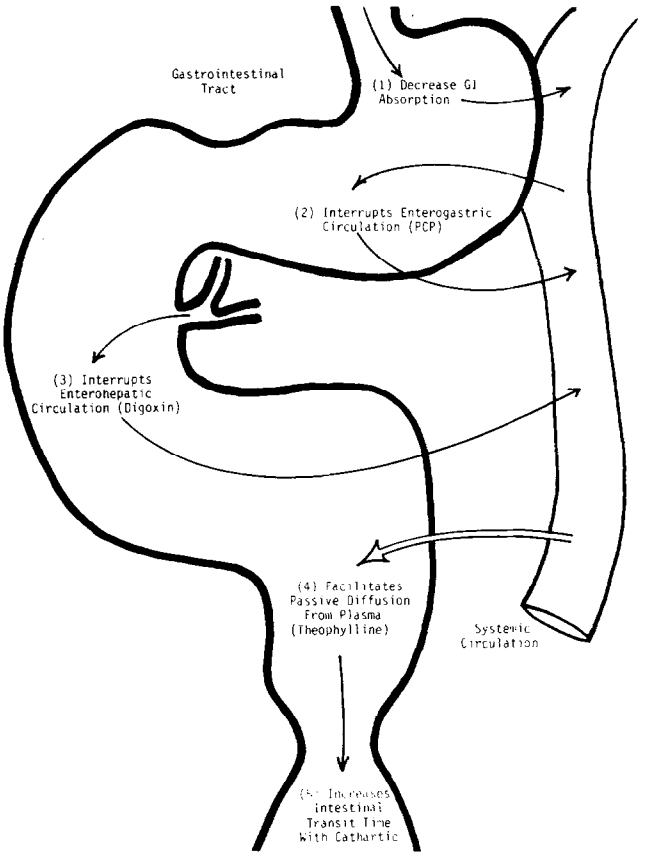

FIGURE 1. Mechanisms by which repetitive doses of activated charcoal may enhance drug elimination.

CLINICAL EXPERIENCE

Any active method of toxin removal must increase the clearance of a drug by at least 30% before it can be considered effective treatment.[32,33] In experimental studies, multiple doses of activated charcoal shortened the half-life and significantly increased the clearance of tricyclics, phenobarbital, cardiac glycosides, theophylline, phenylbutazone and carbamazepine, following normal doses in volunteers.[7,31,34–36] Therapeutic doses used in these studies may not accurately reflect the same pharmacokinetics as toxic doses of the same substance. However, this initial data produced reports of similar findings in patients following overdoses of numerous drugs (Table 3).

Tricyclic antidepressants, such as nortripyline and amitriptyline, are encountered frequently in acute drug poisoning. Hemodialysis and hemoperfusion are seldom effective because of the large volumes of distribution and slow mobilization from the tissues.[7] Their enterohepatic recirculation acts to lengthen the elimination half-life of these drugs from the blood.[37] Older data have shown that repeated doses of activated charcoal, given 30 minutes to six hours after a single nortripyline dose, reduces the drug's blood levels.[52]

TABLE 3. Toxins Removed by Repetitive Charcoal Therapy*

Compound	Percentage Increase in Drug Clearance†	Reference
Amitriptyline	496	37
Carbamazepine	82	38
Chlordecone	106	39
Cyclosporin	233	40
Dapsone	90	41
Digitoxin	800	42
Digoxin	421	43
Digoxin (IV)	47	36
Meprobamate	151	44
Methotrexate (IV)	58	45
Nadolol	34	29
Organic solvents	—	46
Phencyclidine	—	47
Phenobarbital	158	48
Phenobarbital (IV)	173	31
Phenylbutazone	40	38
Salicylate (IV)	38	49
Theophylline	191	50
Theophylline (IV)	104	51

*All toxins were administered orally unless otherwise indicated.
†Estimated percentage increase in total body clearance of toxin.

Twelve volunteers were used to demonstrate reductons in peak levels and the amount of total drug absorbed (measured from the area under the time versus drug concentration curve). In a similar crossover study with healthy volunteers,[35] repeated doses of charcoal between three and 24 hours after doxepin increased the clearance of desmethyldoxepin, the main metabolite of doxepin. The rate of doxepin elimination, however, was not increased significantly. A more limited study involving tricyclic toxicity, reviewed three cases of amitriptyline overdose and indicated shortening of the half-life to less than 10 hours with serial charcoal administration (as compared with previously reported elimination half-lives of 36 to 60 hours).[37]

Digitalis glycosides are highly toxic and have large volumes of distribution. In one patient who ingested 10 mg of digitoxin, the half-life of the glycoside was reduced from 162 hours to 18 hours during repetitive charcoal dosing (60 g every eight hours for three days).[42] Recently, the effect of charcoal on intravenous digoxin kinetics was evaluated in 10 volunteers.[36] Digoxin clearance increased an average of 47% during treatment, and the half-life shortened from 36.5 to 21.5 hours, probably through the interruption of the enterohepatic cycle.[36]

Theophylline is a commonly used drug that has a narrow therapeutic range. The current therapy of severe theophylline toxicity includes charcoal or resin hemoperfusion, or conventional hemodialysis.[50] Berg et al.[31] reported the half-life of theophylline in volunteers to be shortened to approximately half the control value when repeated doses of charcoal were added to the regimen. Mahutte et al.[51] also demonstrated a decrease in serum theophylline half-life from 10.2 to 4.6 hours and increased mean clearance of theophylline from 35.6 to 72.6 ml/kg/h after addition of 30 g oral charcoal every two hours. Case reports of theophylline elimination in acute overdose present similar reductions of serum half-lives to 5.7 and 5.9 after treatment (50 g charcoal every six hours).[50,51] The concentration gradient between blood perfusing the GI tract and the intraluminal charcoal, together with the adsorptive properties of charcoal, is probably responsible for the enhanced clearance.[32]

The effect of charcoal therapy on the elimination of phenobarbital was reported by Berg and colleagues in 1982.[31] In this study, the drug was given intravenously to volunteers followed by multiple oral doses of charcoal. Charcoal decreased the serum half-life of phenobarbital from 110 to 45 hours and enhanced the nonrenal clearance of the drug from 52 to 80% of the total body clearance. The first randomized study evaluating the effects of activated charcoal in the treatment of phenobarbital overdose was published recently.[6] Ten comatose patients were randomized to protocols of either single or repeated doses of charcoal and sorbitol. The serum half-life of phenobarbital shortened from 93 to 36 hours during repeated administration of activated charcoal, yet no alteration in clinical outcome (length of coma, duration of intubation) was seen. Although the number of patients involved was small, this report demonstrates the need for larger clinical trials in poisoned patients.

Together, these data suggest that repetitive charcoal therapy can, even when started several hours after exposure, reduce the half-life of ingested or intravenously administered compounds (Table 3). This assessment becomes more complicated when several factors are considered: 1) Certain drugs that produce metabolic complications in poisoned patients are treated more appropriately with hemodialysis, which can correct the acid-base and electrolyte abnormalities associated with these poisons (i.e., aspirin). 2) Poor gram/gram charcoal binding in vitro (Table 1) does not mean charcoal is not effective. Binding milligram amounts may be useful in some intoxications, such as cyanide. 3) Activated charcoal is not a selective agent. Repetitive therapy may also enhance the clearance of parenterally administered medications often used to treat intoxicated patients (i.e., narcotic antagonists, anticonvulsants, antibiotics).[5] 4) The ability of charcoal therapy to remove active metabolites as well as unchanged drug should be kept in mind. 5) The effectiveness of charcoal therapy may be reduced in patients with impaired GI motility or blood perfusion.[5]

In view of the potential benefit and minimal risk (high therapeutic to risk ratio) we recommend that activated charcoal be administered every four hours in overdoses involving parenteral drugs, toxins with prolonged half-lives, or known

enterohepatic circulation (i.e, phencyclidine, theophylline, digoxin, tricyclics) until serum concentrations are within normal limits and the patient is clinically stable.[11] Until more clinical data are available, administration of activated charcoal should not be relied on as the sole treatment of the intoxicated patient. Standard procedures to increase drug clearance, such as diuresis, alkalinization of urine, and dialysis may be used concurrently with charcoal therapy when indicated.[5]

COMPLICATIONS

There appears to be no inherent toxicity associated with the administration of therapeutic doses of activated charcoal.[7,20] In clinical experiments, uremic patients have been given oral doses of 20 to 50 g activated charcoal per day for up to 20 months without any side effects observed.[53] Similarly, studies of toxicity with respect to prolonged skin contact have shown no detectable harmful effects.[54] Because activated charcoal is a nonreactive substance, its adverse effects seem limited to constipation and occasional vomiting.[7,55]

Although rapid administration may cause vomiting,[55] only two cases of serious aspiration have been reported. An 8-month-old child aspirated charcoal along with gastric contents after its administration through a nasogastric tube.[56] The patient developed protracted respiratory insufficiency characterized by severe bronchospasm. The second case involved a 29-year-old man who aspirated charcoal during extubation and could not be resuscitated.[57] Charcoal particles are inert and do not produce an inflammatory reaction if aspirated into the lungs.[20] However, airway protection should be insured whenever charcoal therapy is used. Obtunded patients may require intubation with a cuffed endotracheal tube or a properly fitted uncuffed endotracheal tube in the younger patient.[56]

CATHARTICS

It is customary to administer a cathartic (saline or osmotic laxative) together with the charcoal to prevent constipation or impaction, and hasten the elimination of the activated charcoal/toxin complex from the bowel.[8] This minimizes the chance for toxins to desorb from the charcoal in the gut. In terms of speed, sorbitol eliminated charcoal stool more rapidly in volunteers than did other cathartics, such as magnesium citrate or sulfate.[8] Investigations in rats showed that administration of a charcoal–70% sorbitol mixture increased the total body elimination of four test drugs more than the administration of either charcoal or sorbitol alone.[23] Furthermore, storage of activated charcoal in sorbitol for as long as one year did not reduce the antidotal efficiency of the absorbent.[23]

Current recommendations suggest using the charcoal–sorbitol mixture until the first black stool appears and thereafter alternating aqueous and sorbitol suspensions.[58] The premixed solution contains 86 g of sorbitol and 30 g of charcoal and is typically administered as commercially packaged (3 g/kg sorbitol). In children, half of the activated charcoal dose may be given as a 70% sorbitol mixture and the other half as aqueous slurry (1.5 g/kg sorbitol).[58]

All patients on multiple dose regimens, especially children, should be closely monitored for fluid and electrolyte depletion. In addition, saline cathartics (sodium, phosphate, and magnesium) are relatively contraindicated in patients with renal disease, electrolyte imbalance, hypertension, bowel obstruction, and congestive heart failure.[59]

CONCLUSIONS

Activated charcoal has found a renewed role in the management of overdosed patients. Once administered to reduce gastrointestinal absorption of many drugs, it increasingly is recommended as a noninvasive means of enhancing drug removal from the blood.[50] Repeated charcoal dosing is inexpensive, effective, simple to administer, and may obviate the need for more invasive methods of toxin removal.

Continuing efforts to make activated charcoal more palatable and deliverable remain warranted. Further controlled, randomized trials are needed to determine how clinical outcomes are affected by multiple doses of charcoal and to identify other compounds (i.e., pesticides, bacterial toxins, industrial chemicals) for which this therapy will be useful. In addition, new modified charcoals may increase the adsorptive capacity of each gram of charcoal.[2]

In acute poisoning, the drug history is often unreliable and overtreatment necessary to avoid late complications. An initial loading dose of activated charcoal (1 mg/kg body weight) should be given as soon as possible after ingestion, but even delayed therapy with repeated doses of charcoal (0.5 mg/kg body weight) is indicated until the results of toxicologic screens are available or the patient is clinically stable. Multiple dose therapy every four hours may prevent the delayed absorption of drugs, inhibit their release from charcoal, and increase their rate of elimination.

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