Chapter A1: Activated Charcoal

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INTRODUCTION

Activated charcoal (AC) is an excellent nonspecific adsorbent. Conclusions regarding the role of AC in poison management are achieved through the integration of pharmacologic data, controlled volunteer trials, studies in heterogeneous patients with overdose or poisoning, and clinical experience. Activated charcoal is provided to a patient after a risk-to-benefit assessment of the presumed ingested xenobiotic and patient-specific factors and circumstances. Benefits include preventing absorption or enhancing elimination by blocking enterohepatic or enteroenteric recirculation of a potentially toxic xenobiotic; risks include vomiting and subsequent aspiration pneumonitis. A detailed discussion of the merits of AC as a decontamination strategy is presented in Chap. 5.

HISTORY

Charcoal a fine, black, odorless powder, has been recognized for more than two centuries as an effective adsorbent of many substances. Organic chemist Scheele first used charcoal to absorb gases in 1773 and was followed in 1791 by Lowitz's use of charcoal with colored liquids.[6,89] Bertrand attributed his survival in 1811 from separate mercuric chloride and arsenic trioxide ingestions to their antecedent admixture with charcoal.[119] In 1830, the French pharmacist Touery demonstrated the powerful adsorbent qualities of charcoal by ingesting several lethal doses of strychnine mixed with charcoal in front of colleagues, suffering no ill effects.[6] An American physician, Holt, first used charcoal to "save" a patient from mercury bichloride poisoning in 1834.[6,89] However, it was not until the 1940s that Andersen began to systematically investigate the adsorbency of charcoal and unquestionably demonstrate that charcoal is an excellent, broad-spectrum gastrointestinal (GI) adsorbent.[6-8]

PHARMACOLOGY

Chemistry and Preparation

Activated charcoal is produced in a two-step process, beginning with the pyrolysis of various carbonaceous materials such as wood, coconut, petroleum, or peat to produce charcoal. This processing is followed by treatment at high temperatures (600°–900°C) with a variety of oxidizing (activating) agents such as steam,

carbon dioxide, or acids to increase adsorptive capacity through formation of an internal maze of pores.[30,60,121] Typical AC surface areas average 800 to 1,200 m^2/g.[117]

Mechanism of Action

The actual adsorption of a xenobiotic by AC relies on hydrogen bonding, ion–ion, dipole, and van der Waals forces, suggesting that most xenobiotics are best adsorbed by AC in their dissolved, nonionized form.[30,63,117,151]

Pharmacokinetics

Activated charcoal is pharmacologically inert and unabsorbed. Its GI transit time is influenced by the type and quantity and ingested xenobiotic, fasting and hydration status, perfusion, and the use of associated cathartics or evacuants, among other factors. The transit of AC is superimposed on a wide range of interindividual variation in gastric emptying and small bowel transit times, even in healthy volunteers.[62] In six volunteers acting as their own controls, AC alone or administered with sodium chloride, sodium sulfate, magnesium sulfate, or a proprietary cathartic "salt" (36.7% anhydrous citric acid, 17.65% magnesium sulfate, and 45.6% sodium bicarbonate), the GI transit times to fecal evacuation ranged from 29.3 ± 1.2 hours to 17.3 ± 1.9 hours.[120] In 59 overdose patients compared with 104 overdose historical control participants who ingested acetaminophen (APAP), carbamazepine, cyclic antidepressants, opioid–APAP combinations, and phenytoin, the addition of 70% sorbitol solution to 25 to 50 g of AC decreased the median half-lives for gastric emptying (from 100 to 82 minutes), small intestinal transit (from 209 to 180 minutes), and orocecal transit (from 270 to 210 minutes).[1,2]

Pharmacodynamics

The adsorption rate to AC depends on external surface area, and the adsorptive capacity depends on the far larger internal surface area.[30,31,110] The adsorptive capacity is modified by altering the size of the pores. Current AC products have pore sizes that range from 10 to 1,000 angstroms (Å), with most of the internal surface area created by 10- to 20 Å-sized pores.[30,32] Most xenobiotics are of moderate molecular weight (100–800 Da) and adsorb well to pores in the range of 10 to 20 Å. Mesoporous charcoals with a pore size of 20 to 200 Å have a greater capacity to adsorb larger xenobiotics as well as those in their larger hydrated forms but are not available for clinical use.[86]

When the AC surface area is large, the adsorptive capacity is increased, but affinity is decreased because van der Waals forces and hydrophobic forces diminish.[151] According to the Henderson-Hasselbalch equation, weak bases are best adsorbed at basic pHs, and weak acids are best adsorbed at acidic pHs. For example, cocaine, a weak base, binds to AC with a maximum adsorptive capacity of 273 mg of cocaine per gram of AC at a pH of 7.0; this capacity is reduced to 212 mg of cocaine per gram of AC at a pH of 1.2.[85] Activated charcoal binds amitriptyline hydrochloride with adsorption capacities of 120 and 100 mg per gram of AC in simulated

gastric and intestinal fluids, respectively.[150] The adsorption to AC of a weakly dissociated metallic salt such as mercuric chloride ($HgCl_2$) decreases with decreasing pH because the number of complex ions of the type $HgCl_3$ and $HgCl_4$ increases, and the number of electroneutral molecules ($HgCl_2$) is reduced.[7] Nonpolar, poorly water-soluble organic substances are more likely to be adsorbed from an aqueous solution than polar, water-soluble substances.[30] Among the organic molecules, aromatics are better adsorbed than aliphatics; molecules with branched chains are better adsorbed than those with straight chains; and molecules containing nitro groups are better adsorbed than those containing hydroxyl, amino, or sulfonic groups.[30]

Activated charcoal decreases the systemic absorption of most xenobiotics, including APAP, aspirin, barbiturates, cyclic antidepressants, phenytoin, theophylline, and other inorganic and organic materials.[49,106,123] Notable xenobiotics not amenable to AC are the alcohols, acids, alkalis, iron, lead, lithium, magnesium, potassium, and sodium salts.[53] Although the binding of AC to cyanide is less than 4%, the toxic dose is small, and 50 g of AC would theoretically be able to bind more than 10 lethal doses of potassium cyanide. Activated charcaol is capable of rapidly removing volatile anesthetic gases such as isoflurane, sevoflurane, and desflurane from anesthetic breathing circuits, which is potentially important in patients who are susceptible to or develop malignant hyperthermia.[14]

The efficacy of AC is directly related to the quantity administered. The effect of the AC to drug ratio on adsorption was demonstrated both in vitro and in vivo with para-aminosalicylate (PAS). In vitro, the fraction of unadsorbed PAS decreased from 55% to 3% as the AC-to-PAS ratio increased from 1:1 to 10:1 at a pH of 1.2.[114] This study provides the best scientific basis for the 10:1 AC-to-drug ratio dose typically recommended. In human volunteers, as the AC-to-PAS ratio increased from 2.5:1 to 50:1, the total 48-hour urinary excretion decreased from 37% to 4%.[114] Presumably, this occurred because more of the PAS was adsorbed by AC in the lumen of the GI tract rather than being absorbed systemically. These same studies demonstrate AC saturation at low ratios of AC to drug and argue for a 10:1 ratio of AC to xenobiotic. A meta-analysis of 64 controlled volunteer studies demonstrated that the percentage of reduction in drug exposure provided by AC followed a sigmoidal dose–response curve.[69] Activated charcoal to drug ratios of 1:1, 5:1, 10:1, 20:1, 25:1, and 50:1 reduced drug exposures by 9.0%, 30.2%, 44.6%, 58.9%, 62.9%, and 73.0%, respectively.[69] In a subsequent study of volunteers ingesting 50 mg/kg of APAP, reducing a 1-hour postingestion 50 g AC dose to 25 or 5 g caused the APAP area under the concentration versus time curve (AUC) to increase by 23.6% and 59.0%, respectively.[55]

In vitro studies demonstrate that adsorption begins within about 1 minute of AC administration but does not achieve equilibrium for 10 to 25 minutes.[31,106] The clinical efficacy of AC to prevent absorption is inversely related to the time elapsed after ingestion and depends largely on the rate of absorption of the xenobiotic. According to a meta-analysis of volunteer studies, the median reductions of drug exposure when AC was administered at 0 to 5 minutes, 30 minutes, 60 minutes, 120 minutes, 180 minutes, 240 minutes, and 360 minutes after ingestion were 88.4%, 48.5%, 38.4%, 24.4%, 13.6%, 27.4%, and 11%, respectively.[69] Early AC administration is more important with rapidly absorbed xenobiotics, in which AC functions to prevent

xenobiotic absorption by achieving rapid adsorption in the GI tract. After a xenobiotic is systemically absorbed or parenterally administered, AC can enhance elimination through enterohepatic and enteroenteric recirculation as opposed to affecting absorption.

Desorption (drug dissociation from AC) can occur, especially weak acids, as the AC–drug complex transits the stomach and intestine and as the pH changes from acidic to basic.[50,113,147] Whereas strongly ionized and dissociated salts, such as sodium chloride and potassium chloride, are poorly adsorbed, nonionized or weakly dissociated salts, such as iodine and mercuric chloride, respectively, are adsorbed. Binding of g-hydroxybutyrate (800 mg) to AC (10 g) decreased from 84.3% to 23.3% when exchanging simulated gastric for intestinal fluid.[105] Diminished AC adsorptive capacity in the intestinal lumen can also occur because of the rapid adsorption by AC of intestinal fatty acids, which rapidly cover the surface of carbon granules.[89] Desorption can lead to ongoing systemic xenobiotic absorption over days. In this case, the apparent elimination half-life of the xenobiotic increases, but peak concentrations remain unaffected.[111] The clinical effects of desorption can be minimized by providing sufficient AC to overcome the decreased affinity of the xenobiotic secondary to pH change, such as by using multiple-dose AC (MDAC).[73,96,109,124,140] Although ethanol and other solvents such as polyethylene glycol (PEG) are minimally adsorbed by AC, they can decrease AC adsorptive capacity for a coingested xenobiotic by competing for AC binding.[12,111,113,115]

Concomitant Administration of Activated Charcoal with Cathartics or Evacuants

Cathartics are often used with AC; however, evidence suggests that AC alone is comparably effective to AC plus a single dose of cathartic (sorbitol or magnesium citrate).[3,73,90,92,96,104,110,122] If a cathartic is used, it should be used only once. Repeated doses of magnesium-containing cathartics are associated with hypermagnesemia,[99,142] and repeated doses of any cathartic are associated with salt and water depletion, hypotension, and severe or fatal fluid and electrolyte derangements.[48] Activated charcoal with sorbitol is not recommended for children younger than 1 year of age.[121]

Whole-bowel irrigation (WBI) with PEG electrolyte lavage solution can significantly decrease the in vitro and in vivo adsorptive capacity of AC, depending on the individual xenobiotic, its formulation, and the GI location. For example, experiments demonstrate desorption of cocaine, fluoxetine, salicylate, and theophylline from AC,[10,76,85] but chlorpromazine was not significantly affected by PEG at gastric pH.[11] A controlled crossover study compared the addition of a short course of WBI (1 L/h) with AC alone in nine healthy participants who were provided simultaneous carbamazepine (200 mg), theophylline (200 mg), and verapamil (120 mg).[80] Polyethylene glycol decreased AC's efficacy for carbamazepine and theophylline but was synergistic with AC for verapamil.[80] Whole-bowel irrigation did not improve upon AC's nonstatistically significant 11% decrease in absorption in volunteers ingesting 2.88 g of aspirin.[91] The most likely explanation is competition by PEG for the surface of the AC for solute adsorption. Activated charcoal and WBI interactions are further discussed in Antidotes in Depth: A2.

Related Formulations

Porous carbon microsphere compounds (eg, AST-120) are clinically used to adsorb endogenous enteric uremic toxins to mitigate glomerular hypertrophy, interstitial fibrosis, and progression of chronic kidney disease.[136,137,161]

ROLE OF ACTIVATED CHARCOAL IN GASTROINTESTINAL DECONTAMINATION

Single-Dose Activated Charcoal

It is difficult to assess the efficacy of single-dose AC (SDAC) in a prospective study involving consecutive adults receiving 50 g of AC for self-poisonings because of the exclusions of multiple xenobiotic and sustained-release products and because SDAC was used in combination with other forms of GI decontamination in all symptomatic patients.[97] Not surprisingly, a beneficial effect of SDAC on outcome measures could not be demonstrated in asymptomatic patients. Similarly, a study of routine SDAC administration after oral overdose consisting primarily of benzodiazepines, APAP, and selective serotonin reuptake inhibitors could not demonstrate differences in mortality, length of stay, vomiting, or intensive care admissions.[33] A prospective trial of 876 patients comparing SDAC alone with SDAC plus gastric emptying was unable to demonstrate a difference in outcomes, with the exception of patients presenting within 1 hour of ingestion, although this difference was not sustained after being adjusted for severity.[127] Subsequent studies touting the lack of benefit of AC are of limited value because of similar design flaws such as including irrelevant exposures or those to which AC would not adsorb or conflating AC administration outcomes with orogastric lavage.[118] When evaluating SDAC alone, a meta-analysis of 64 controlled volunteer studies found significant reductions in ingested xenobiotic amounts when SDAC was provided in appropriate quantity (eg, a 10:1 AC: xenobiotic ratio) and within 240 minutes of exposure.[69]

Research subsequent to this meta-analysis has sustained primarily pharmacokinetic advantage of SDAC, although some improvements in clinically important endpoints were demonstrated. A healthy volunteer study in 12 patients in which SDAC was provided 15 minutes after supratherapeutic APAP ingestions (60 mg/kg) reduced APAP absorption by a mean of 41%.[154] In nine human volunteers ingesting 5 g of APAP and 0.5 mg/kg of oxycodone, 50 g of SDAC at 1, 2, or 3 hours reduced the APAP AUC by 43%, 22%, and 15%, respectively.[103] In six volunteers, concentrations of lamotrigine (100 mg); oxcarbazepine (600 mg); and oxcarbazepine's active metabolite, 10,11-dihydro-10-hydroxy-carbamazepine were reduced by 42%, 97.2%, and 95.8%, respectively, by 50 g of AC provided 30 minutes after ingestion.[74]

In a pharmacokinetics and pharmacodynamics evaluation of escitalopram overdosed patients, SDAC reduced the absorbed fraction by 31% and reduced the risk of QT prolongation by approximately 35% for escitalopram doses above 200 mg.[152] In 319 patients with 436 venlafaxine overdoses, SDAC or SDAC with WBI significantly decreased the odds of seizure to 0.48 and 0.25, respectively, compared with no

decontamination.[79] In 176 patients presenting with 286 separate quetiapine overdoses, SDAC administration within 2 hours reduced the probability of intubation by 7% for a 2-g ingestion and by 17% for a 10-g ingestion, although time to extubation was unaffected.[67] In pharmacokinetic modeling study of sertraline overdose that was limited by uncertainty in ingestion time and dose, SDAC decreased the AUC and decreased the maximum plasma concentration when administered between 1 and 4 hours after overdose.[34] Volunteer studies evaluated late AC administration in factor Xa inhibitor ingestions. Activated charcoal decreased ingested rivaroxaban AUCs by 43%, 31%, and 29% when administered 2 hours, 5 hours, and 8 hours postdose, respectively.[116] Similarly, for apixaban, which undergoes enteroenteric recirculation, AC decreased AUCs by 50% and 28%, when administered 2 hours and 6 hours postdose, respectively, as well as decreasing its apparent half-life from 13.4 hours to approximately 5 hours.[155] A retrospective observational study showed neither benefit nor harm of AC in organic phosphorus compounds or carbamate poisoning.[101] In light of further pharmacokinetic understanding and the potential for larger ingestions, more recent recommendations have relaxed the narrow AC administration "window" to support its utilization beyond 1 hour. This is true even in cases of ingestions for which an antidote exists, such as APAP.[20,25,118]

Multiple-Dose Activated Charcoal

Multiple-dose AC functions both to prevent the absorption of xenobiotics that are slowly absorbed from the GI tract and to enhance the elimination of suitable xenobiotics that have already been absorbed. Multiple-dose AC decreases xenobiotic absorption when large amounts of xenobiotics are ingested and dissolution is delayed (eg, masses, bezoars), when xenobiotic formulations exhibit a delayed or prolonged release phase (eg, enteric coated, extended release), when GI motility is impaired because of coingestants, or when reabsorption can be prevented (eg, enterohepatic circulation of active xenobiotic, active metabolites, or conjugated xenobiotic hydrolyzed by gut bacteria to active xenobiotic).

The ability of MDAC to enhance elimination after absorption had already occurred was first reported in 1982.[13] This report concluded that orally administered MDAC enhanced the total body clearance (nonrenal clearance) of six healthy volunteers given 2.85 mg/kg of body weight of intravenous (IV) phenobarbital.[13] The serum half-life of phenobarbital decreased from 110 ± 8 to 45 ± 6 hours. An editorial suggested that MDAC enhanced the diffusion of phenobarbital from the blood into the GI tract and trapped it there for later fecal excretion. In this manner, AC was said to perform as an "infinite sink," allowing for "gastrointestinal dialysis" to occur.[81] These findings were confirmed by studies in dogs and rats using IV aminophylline and shown to be independent of theophylline enterohepatic circulation.[39,78,94] Subsequent studies using MDAC with IV aminophylline further extended these results to humans.[64] Using an isolated perfused rat small intestine, the concept of GI dialysis[94] was elegantly demonstrated because AC dramatically affected the pharmacokinetics of theophylline and produced a constant intestinal clearance that approximated intestinal blood flow.[94] In 114 hemodialysis patients who received a mean AC daily dose of 3.19 ± 0.81 g/day in three divided doses, mean serum phosphate concentrations decreased by 2.60 ± 0.11 mg/dL, further supporting the concept of "GI dialysis."[156]

The toxicokinetic considerations underlying MDAC's ability to enhance elimination are similar to those involved in deciding whether hemodialysis would be appropriate for a given xenobiotic. Successful MDAC requires the xenobiotic to be in the blood compartment (low volume of distribution), have limited protein binding, and have prolonged endogenous clearance. Experimental evidence suggests a role for MDAC in the absence of available Prussian blue (Antidotes in Depth: A31) to treat thallium poisoning.[59] Although MDAC increases to varying degrees the elimination of amitriptyline, cyclosporine,[61] carbamazepine,[15,17,157] dapsone,[108] digitoxin,[35,126] nadolol,[43] nortriptyline,[36] phenobarbital,[128] phenylbutazone,[107] propoxyphene,[71] quinine,[28] salicylate,[58,75] and theophylline,[14,84,146] its clinical utility remains to be defined.[28,72,145]

An analysis of 28 volunteer studies involving 17 xenobiotics was unable to correlate the physical chemical properties of a particular xenobiotic with MDAC's ability to decrease the plasma half-life of that xenobiotic.[22] Although the half-life was not thought to be the best marker of enhanced elimination, it was the only parameter consistently evaluated in these exceptionally diverse studies. The xenobiotics with the longest intrinsic plasma half-lives seemed to demonstrate the largest percent reduction in plasma half-life when MDAC was used. A subsequent animal model with therapeutic doses of four simultaneously administered IV xenobiotics (APAP, digoxin, theophylline, and valproic acid) clarified the role of pharmacokinetics on MDAC's effectiveness.[27] Theophylline, APAP, and valproic acid all have small volumes of distribution. However, of the three, only valproic acid is highly protein bound at the doses used, which probably accounted for MDAC's inability to increase its clearance while increasing clearance of the three other xenobiotics. However, volunteer studies do not accurately reflect the overdose situation[95] in which saturation of plasma protein binding, saturation of first-pass metabolism, and acid–base disturbances may make more free xenobiotic available for an enteroenteric effect and therefore more amenable to MDAC use. The most rapid and dramatic effect of MDAC was on theophylline clearance. Large volumes of distribution alone do not necessarily exclude MDAC's benefit. Although digoxin has a large volume of distribution, it requires several hours to distribute from the blood to the tissues. Multiple-dose AC is beneficial as long as the digoxin remains in the blood compartment and distribution is incomplete.

In one case series of infants with aminophylline and theophylline overdoses, MDAC appeared to reduce theophylline half-lives (2–12 hours) compared with historical values.[138] Multiple-dose AC added as an adjunct to phototherapy in neonatal hyperbilirubinemia produced a significantly greater decline in bilirubin concentrations than in those receiving phototherapy alone.[5] In a randomized clinical study, patients with phenobarbital overdoses were given SDAC or MDAC.[128] Although the phenobarbital half-life was significantly decreased in the MDAC group (36 versus 93 hours), the length of intubation time required by each group did not differ from one another. This study was criticized for small size, unevenly matched groups, and focus on a single endpoint (extubation) potentially dependent on factors other than patient condition (eg, the time of day). In 15 adult patients with supratherapeutic phenytoin concentrations, MDAC reduced the time to phenytoin concentration less than 25 mg/L from 41.1 to 19.3 hours, although clinical endpoints were again

unchanged.[141] Multiple-dose AC markedly decreased the apparent phenytoin half-lives in patients with prolonged half-lives because of CYP2C9 enzyme genetic polymorphisms.[23]

A compelling demonstration of MDAC's benefits in the overdose setting comes from a study performed in Sri Lanka in patients with severe cardiac toxicity caused by intentional overdose with yellow oleander seeds.[38] An initial AC dose of 50 g was administered to all patients, who were then randomized to 50 g of AC every 6 hours for 3 days or placebo. There were statistically fewer deaths and fewer life-threatening dysrhythmias in the MDAC group. Subsequent randomized, controlled trials further evaluated no AC, SDAC, and MDAC in self-poisoned patients. In 104 patients ingesting yellow oleander seeds in Sri Lanka, despite erratic and prolonged absorption, SDAC and MDAC significantly and equivalently reduced cardiac glycoside 24-hour mean residence time (which quantifies the time course of a xenobiotic through the body) from 11.21 ± 1.55 hours (no AC) to 10.36 ± 1.14 hours (SDAC) and 10.20 ± 0.99 hours (MDAC), respectively, and apparent terminal half-life from 62.9 hours (no AC) to 33.9 hours (SDAC) and 32.3 hours (MDAC), respectively.[131] Despite this, neither SDAC nor MDAC reduced the mortality rate among 4,629 randomized, poisoned patients.[44] However, in this study, about one-third of the patients had ingested yellow oleander seeds, slightly less than one-third ingested pesticides, and mechanical forced emesis or gastric lavage occurred in 54.0% and 7.5% of patients prerandomization.[44] It is unclear how these trials apply to management in developed countries, where the use of antidotes such as digoxin-specific antibody fragments for cardioactive steroid poisoning and atropine and pralidoxime for organic phosphorus pesticide poisoning routinely complement GI decontamination and the absorption kinetics of most prescription medications differ from the substances ingested in the trial.[68] A systematic review concluded that MDAC could enhance phenobarbital or primidone elimination in severe poisonings, although supportive care is the relevant clinical intervention.[130]

Ultimately, the decision to administer SDAC or MDAC should involve a patient-tailored, risk-to-benefit analysis. Potential adverse effects are weighed against the particular ingested xenobiotic, its quantity, and formulation; dose–response curve of the xenobiotic; the impact of SDAC or MDAC on this curve; the time since ingestion; coingestants; gastric motility and contents; available antidotes, therapies, and medical support; the severity of presentation; anticipated sequelae; patient cooperativity; and other patient-specific factors and comorbidities.[68,117,121,143]

ADVERSE EFFECTS AND SAFETY ISSUES

Contraindications to AC include presumed GI perforation or discontinuity or the need for endoscopic visualization (eg, in caustic ingestions). To prevent aspiration pneumonitis from oral AC administration, an airway assessment must occur, and potential airway compromise should be excluded. Subsequently, a risk-to-benefit assessment with regard to the need for airway protection and the need for AC should be made. Other considerations include a determination of adequate GI motility (appropriate bowel sounds to ensure peristalsis) and normal abdominal examination findings and absent distension or signs of an acute

abdomen. With compromised bowel function, AC should be withheld or delayed until the stomach can be decompressed to decrease the risk of subsequent vomiting and aspiration.

Although the use of AC is relatively safe, emesis, which typically occurs after rapid administration; constipation; and diarrhea are frequently reported after AC administration.[110] Constipation and diarrhea are more likely to result from the ingestion itself than from the AC. However, black stools that are negative for occult blood, black tongues, and darkened mucous membranes are frequently observed. Serious adverse effects of AC include pulmonary aspiration of AC with or without gastric contents, leading to airway obstruction (potentially of rapid onset), acute respiratory distress syndrome, bronchiolitis obliterans, and death;[9,40,47,52,57,70,117,121,125,139] peritonitis from spillage of enteric contents, including AC, into the peritoneum after GI perforation;[88] and intestinal obstruction and pseudo-obstruction, especially after repeated AC doses in the presence of either dehydration or prior bowel adhesions.[19,54,83,98,158] Although a significant number of patients aspirate gastric contents before endotracheal intubation and AC administration,[100,132] the incidence of AC aspiration after endotracheal intubation varies from 4% to 25%, depending on the nature of the study. Another retrospective investigation demonstrated a 1.6% incidence of aspiration pneumonitis in unselected overdosed patients. Altered mental status, spontaneous emesis, and cyclic antidepressant overdose were associated risk factors; AC was not in itself a risk factor.[66] Because sorbitol is hepatically metabolized to fructose, the package insert warns against administration of AC with sorbitol to patients with a genetic intolerance to fructose.[121]

Adverse Effects of Multiple-Dose Activated Charcoal

Complications observed with SDAC increase with MDAC. Other adverse effects of MDAC include diarrhea when multiple sorbitol-containing AC preparations are used, constipation, vomiting with a subsequent risk of aspiration, intestinal ileus and obstruction, and a reduction of serum concentrations of therapeutically used xenobiotics.[42,98,117,125] One retrospective review of 834 poisoned patients uncontrolled for type of ingestion found that MDAC was associated with clinically significant pulmonary aspiration in 0.6%, GI obstruction in 0%, hypernatremia in 6.0%, and hypermagnesemia in 3.1%.[42] Administration of multiple sorbitol-containing AC preparations infrequently produces salt and water depletion, hypotension, and potentially fatal electrolyte derangements, especially in children.[48,102]

PREGNANCY AND LACTATION

The safety in pregnancy category for AC is undetermined. The benefit of preventing absorption with AC should outweigh the risk of administration to the pregnant patient. The underlying elevated prevalence of nausea and vomiting in pregnancy[77] might predispose pregnant patients to a potentially higher rate of vomiting, although this is speculative. Single-dose AC and MDAC have been safely administered to pregnant patients as part of poisoning management.[18,26,37,93,133] Murine and lapine studies have not demonstrated

any teratogenic risk.[121] The lack of absorption of AC would not predispose it to breast milk excretion, although definitive safety in lactation has not been established.[121]

DOSING AND ADMINISTRATION

Single-dose AC should be administered when a xenobiotic is still expected to be available for adsorption in the GI tract and the benefit of preventing absorption outweighs the risk. The optimal SDAC dose is unknown.[28] However, most authorities recommend a minimum AC dose of 1 g/kg of body weight or a 10:1 ratio of AC to xenobiotic, up to an amount that can be tolerated by the patient and safely administered, which usually represents 50 to 100 g in adults. For some ingestions (eg, salicylate or APAP), a 10:1 ratio would be impracticable to achieve, although the 1-g/kg dose appears to be efficacious. This is supported by volunteer studies of supratherapeutic ingestions.[55,69] Activated charcoal that is not premixed is best administered as a slurry in a 1:8 ratio of AC to suitable liquid, such as water or cola.

Prehospital Administration

Prehospital AC administration by emergency medical personnel expedites the administration after overdose.[4,159] However, the implementation costs and potential adverse effects have to be weighed against the small number of patients who would actually benefit.[65] In a study simulating home administration in 50 young children, 86% readily drank the AC–water slurry, and 76% of them consumed 95% to 100% of the total dose.[21] Of seven children in a simulated home environment administered AC in regular cola, three drank 1 g/kg, two drank about half of this therapeutic dose, and the other two drank very little.[134] A prospective poison control center case series demonstrated successful home AC administration. In this series, the median age of the patients was 3 years, and the median AC dose ingested was 12 g.[144] However, other attempts at getting children to ingest AC were not as successful. Difficulty was noted in 70% of attempts to administer a standard AC dose to children in the home setting.[41] A review of AC in the home suggested variable success depending on the parent and child.[46] A retrospective review of poisoned children concluded that those who were preannounced to an emergency department by the poison control center received AC earlier (59 ± 34 minutes) than patients without a referral (71 ± 43 minutes).[148] One additional retrospective review determined that prehospital paramedic-administered AC did not increase EMS encounter duration.[153]

Hospital Administration

Administration in children is facilitated by offering an opaque, decorated, covered cup and a straw.[160] The black color and gritty nature of AC have led to the development of many formulations to improve palatability and patient acceptance. Bentonite, carboxymethyl cellulose, and starch[56,104,135] are used as thickening agents, and cherry syrup, chocolate syrup, sorbitol, sucrose, saccharin, and ice cream have been used as flavoring agents.[31,82,87,162] Most additives do not decrease the adsorptive capacity; however, improvements in palatability and acceptance have been minimal or nonexistent with all of these formulations.[30] Although a

milk chocolate AC formulation evaluated by children was rated superior in palatability to standard AC preparations,[45] it was never marketed in the United States. A marketed cherry-flavored AC product was rated by adult volunteers as preferable over plain AC, and a statistically significant larger quantity of the flavored AC was ingested.[29] This difference was not maintained in adult overdosed patients; most patients consumed the entire bottle of AC independent of cherry flavoring. Cold cola was used to enhance palatability in volunteer children and adults. Children preferred regular cola over diet cola. Teenagers preferred the palatability of AC mixed with chocolate milk or cola over AC mixed with water, but this did not significantly improve ease of swallowing.[24] Adults rated cola–AC preferable to plain AC.[129,134] Other studies in adult overdosed patients compared different AC brands without additives or flavoring to determine the AC quantity typically ingested.[16,51] In one study, approximately half of the 50 g of AC offered was ingested, and 7% of the patients vomited.[16] In the other study, 60 g of AC as Liqui-Char (standard AC) or CharcoAid G (superactivated granulated AC) was offered, and approximately 95% of each formulation was consumed in 20 minutes. There was no difference in the amount consumed even though the palatability of the granular form of AC (CharcoAid G) was rated higher.[51]

Multiple-Dose Activated Charcoal Administration

An initial AC loading dose should be administered to adults and children in an attempt to achieve a AC-to-xenobiotic ratio of 10:1 or 1 g/kg of body weight (if the xenobiotic exposure amount is unknown). The correct AC dose and interval for multiple dosing, when it is indicated, is best tailored to the amount and dosage form of the xenobiotic ingested, the severity of the overdose, the potential lethality of the xenobiotic, and the patient's ability to tolerate AC. Benefit should always be weighed against risk. Doses of AC for multiple dosing have varied considerably in the past, ranging from 0.25 to 0.5 g/kg of body weight every 1 to 6 hours to 20 to 60 g for adults every 1, 2, 4, or 6 hours. Some evidence suggests that the total dose administered may be more important than the frequency of administration.[64,149] Continuous nasogastric administration of AC is reported, especially when vomiting is a problem, although the risk-to-benefit assessment would require consideration.[50,112,149] After the initial AC loading dose of 1 g/kg, subsequent doses of 0.5 g/kg (~25–50 g in adults) every 4 to 6 hours for up to 12 to 24 hours is reasonable in most circumstances.

FORMULATION AND ACQUISITION

Activated charcoal is supplied in bottles or tubes as a ready-to-use aqueous suspension in multiple doses formulations (eg, suspensions of 15 g, 25 g, and 50 g of AC in 72 mL, 120 mL, and 240 mL at a fixed concentration of 208 mg/mL AC).[121] Some AC suspensions are also premixed with sorbitol (eg, 25 and 50 g AC with 48 or 96 g of sorbitol to yield 208 mg/mL of AC and 400 mg/mL of sorbitol).[121] When not premixed, it is recommended to create a slurry of AC in a 1:8 ratio of AC to suitable liquid (eg, water, cola).

SUMMARY

Activated charcoal is an effective, nonspecific adsorbent.

Absent contraindications, AC should be of benefit to a patient with a potentially life-threatening ingestion of a xenobiotic that is adsorbed by AC and is expected to be present in the GI tract at the time of administration. Activated charcoal does not adsorb alcohols, acids, alkalis, iron, lead, lithium, magnesium, potassium, or sodium salts.

Multiple-dose AC is useful to prevent systemic absorption of xenobiotics with prolonged absorptive phases such as extended-release formulations or enteroenteric recirculation.

In the postabsorptive phase, MDAC decreases the elimination half-lives of certain xenobiotics.

Care must be taken to avoid pulmonary aspiration and intestinal obstruction when administering AC and MDAC.

Home availability of AC should be encouraged in remote locations where prehospital care is not immediately available.

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