Multiple-Dose Activated Charcoal in Treatment of Acute Poisoning

Introduction

Activated charcoal is a black, odorless powder made from vegetable components (coal, coconut shell, peat, wood, or petroleum) and effectively adsorbs many substances.[1-3] The charcoal is "activated" by exposure to gas in high temperatures, or by using phosphic acid and/or zinc chloride.[2]

Activated charcoal has been widely used in previous years, with US poison centers recommending charcoal therapy more than 136,000 times in 1999.[4] Since then use has declined, evidenced by poison centers recommending charcoal about 50,000 times in 2013, reflecting a realization of the limitations and risks associated with use, and decreasing enthusiasm for GI decontamination.[4] Activated charcoal can be administered as a single dose (single-dose activated charcoal – SDAC) or in multiple doses (multiple-dose activated charcoal – MDAC); however, there are differences in administration, indication, and outcome.[4]

This article will discuss the mechanism of action of activated charcoal, the difference between MDAC and SDAC, xenobiotics and poisons for which MDAC has reported efficacy (highlighting aspirin, carbamazepine, and phenytoin), dosing and administration recommendations for MDAC, and potential adverse effects of MDAC.

Activated Charcoal Mechanism of Action

The once activated, the charcoal has an internal pore structure, which enlarges the surface area from 2-4 m^2/g to 1500 m^2/g (activated charcoal for medicine requires surface area of no less than 900 m^2/g).[2] Owing to this large surface area, activated charcoal exerts its mechanism of action by adsorbing many xenobiotics, with the exception of highly ionic salts (iron, lithium, and cyanide) and polar molecules (alcohols).[5] The actual adsorption of substances is believed to

occur through ion-ion, hydrogen bonding, van der Waals, and dipole forces – most substances are best adsorbed in a, non-ionized form.[1]

SDAC vs. MDAC

SDAC is given as a single dose, with the goal of preventing absorption of a potentially toxic xenobiotic, and is thought to have the best results when administered within one hour of the exposure.[1,3-5] In contrast, MDAC is defined as at least two doses of activated charcoal with the goal to enhance elimination of the drug.[2,4,5] MDAC functions to prevent the absorption of xenobiotics that are slowly absorbed from the GI tract, and in some cases, enhance elimination of substances that have already been absorbed.[1]

The effects of SDAC are mostly as described above – to adsorb xenobiotics to prevent systemic absorption, and limit toxic effects. MDAC elicits its effects via a more complex mechanism; it binds xenobiotics that diffuse from the bloodstream into the gut in a process termed "gastrointestinal dialysis".[1,2] Some drugs can reenter the gut via passive diffusion, and as long as a concentration gradient is present, with drug concentration lower in the gut lumen, drug can pass from the bloodstream into the gut lumen and become adsorbed to charcoal.[1,2] MDAC also can prevent ongoing absorption of a xenobiotic that persists in the GI tract.[1,3] It is most effective for pharmacobezoars, and drugs that undergo enterohepatic and enterogastric recirculation – where the drug can be circulated back into the liver, excreted through the bile duct back into the GI tract, and then reabsorbed into the bloodstream.[1]

Drugs, Xenobiotics, and Poisons Studied with MDAC Administration

In 1999, the American Academy of Clinical Toxicology and European Association of Poisons Centres and clinical Toxicologists published a position statement and practice guidelines regarding the use of multiple-dose activated charcoal.[2] For specific drugs where MDAC

administration has been evaluated, they explored animal studies, volunteer pharmacokinetic studies, and clinical studies. They concluded that MDAC should be considered in a potentially fatal ingestion of dapsone, theophylline, phenobarbital, carbamazepine, or quinine. Aspirin and phenytoin also have data demonstrating potential benefit of MDAC, and these drugs – along with carbamazepine – are discussed in-depth below.

Aspirin: 1985 – Hillman et al. report 5 cases of aspirin toxicity with maximum plasma concentrations ranging from 42.5-65.5 mg/dL.[6] The patients were treated with gastric lavage and alkaline diuresis, and they were given 50 g of charcoal every 4 hours until symptoms were resolved. The greatest average clearance rate matched a half-life of less than 3.2 hours. This was compared to 6 control patients, whose plasma half-life was 27 hours. In this study, in all 5 treatment patients, MDAC caused a decrease in plasma salicylate levels. The authors stated it "appeared to be more effective than forced alkaline diuresis".[6]

1990 – Vertrees et al. report 2 pediatric cases of salicylate overdose that had concentrations of 83.6 mg/dL (patient 1) and 76 mg/dL (patient 2).[7] Both patients were given MDAC (via NG tube), and elimination half-life was decreased to 7.2 hours in the first patient, and 5.9 hours in the second patient. The authors concluded that MDAC could be an adjunct therapy to alkalinization of the urine in treatment of aspirin toxicity, as long as it can be shown safe and effective.[7]

1992 – Mayer et al. studied pharmacokinetics of an aspirin suspension in 9 adult volunteers, who each ingested 2880 mg of aspirin in suspension.[8] There were three study arms: control, charcoal (multiple-dose), and WBI (whole bowel irrigation). MDAC and WBI both decreased area under the curve of the drug, but neither was significant. From this study, it appears that MDAC does not increase clearance of absorbed salicylate.[8]

MDAC Probable Efficacy	
Drug	**Conclusion**
Aspirin	"Data insufficient to recommend use of MDAC for aspirin poisoning"[2]
Carbamazepine	MDAC comparable to charcoal hemoperfusion, but "reduction in morbidity has not been demonstrated"[2]
Dapsone	Data supports increased elimination, but no evidence that methemoglobinemia and hemolytic anemia are decreased[2]
Phenobarbital	There is good evidence that total clearance from the body is significantly enhanced by MDAC[2]
Phenytoin	MDAC may enhance elimination, but case reports do not confirm benefit[2]
Quinine	Further studies are needed to establish clinical benefit of MDAC in quinine poisoning[2]
Theophylline	More research is needed to show that morbidity is reduced by MDAC[2]

MDAC Possible Efficacy	
Drug	**Conclusion**
Digoxin/Digitoxin/Yellow Oleander[2,3]	"In severe cases of poisoning, digoxin-specific antibody fragments should be considered"[2]
Meprobamate	"Charcoal therapy may be effective in increasing drug elimination"[2]
Valproic Acid	MDAC could be effective at higher plasma concentrations of the drug, but further studies are needed for confirmation[2]
Vancomycin	The benefit identified in case reports suggests efficacy, but further studies are required to confirm this data[2]

MDAC Unlikely Efficacy	
Drug	**Conclusion**
Methotrexate	The single pharmacokinetic study evaluated does not advocate use of MDAC for methotrexate
Tricyclic Antidepressants	"It would not be expected from the very large volume of distribution . . . that [tricyclic antidepressant] elimination would be enhanced by activated charcoal"[2]

2015 – A guidance document from the American College of Medical Toxicology was published titled, "Management Priorities in Salicylate Toxicity". They recommended that activated charcoal may be considered in patients with early presentation, rising salicylate levels, or other signs of incomplete absorption.[9]

In summary, activated charcoal does not seem to enhance elimination of absorbed salicylate, but it has utility in poisoning situations due to delayed gastric absorption and bezoar formation following massive ingestion.

Carbamazepine: 1992 – Wason et al. report 5 cases (2 acute, 3 chronic) of carbamazepine toxicity. Peak concentrations reported were from 22.4 to 60 mcg/mL. They conclude that activated charcoal administration resulted in a decreased elimination half-life; however, the time to resolution of clinical effects was decreased by the use of MDAC.[10]

1999 – Deshpande et al. in a case report showed that charcoal hemoperfusion effectively decreased carbamazepine concentrations in a 16-month-old patient.[11]

2006 – Brahmi et al. describe 12 patients attempted suicide by ingesting carbamazepine. 6 patients received MDAC and 6 patients received SDAC. The duration of coma (20 vs 29 hrs), mechanical ventilation (24 vs 36 hrs), and length of hospital stay (30 vs 39 hrs) were significantly decreased in the MDAC group.[12]

In summary, MDAC appears to be effective in decreasing the elimination half-life of carbamazepine, and can decrease the time patients spend in the hospital receiving supportive care measures.

Phenytoin: 2012 – Skinner et al. conducted a randomized controlled study in patients presenting to the ED with levels of phenytoin above 30 mg/L.[13] Administration of MDAC was associated with a decreased time to reach subtoxic levels (<25mg/L) from 41.1 hours (control group) to

19.3 hours, which was statistically significant.[13] There were also lower median and range peak levels and MMSE scores (not significant).[13]

2015 – Chan et al. describe three patients with genetic polymorphisms in CYP2C9, who were "poor metabolizers", and were experiencing phenytoin toxicity. Elimination of phenytoin was very slow in these patients (up to 178 hour half-life), and administration of MDAC led to large and rapid reductions in half-life.[14]

In summary, MDAC appears to significantly increase elimination of phenytoin, and may have greater benefit in patients who have a poor metabolizer genotype of CYP2C9.

Dosing and Administration

According to the American Academy of Clinical Toxicology and the European Association of Poisons Centres and Clinical Toxicologists Position Statement, clinical data endorses an initial dose of 50-100 g followed by a dose every 2 or 4 hours at 12.5 g/hour (adults).[2] In pediatric patients, smaller doses (10-25 g) can be considered due to overall smaller ingestions and lesser capacity of the gut lumen.[2] It should be noted that activated charcoal may cause vomiting; thus it may be prudent to give an intravenous antiemetic.[2]

Co-administration of cathartics (sorbitol, mannitol and sodium, magnesium sulfate) with activated charcoal is controversial. Some research suggests that administering cathartics may actually increase absorption of the xenobiotic, and may decrease adsorption to charcoal.[2] In contrast, other evidence shows that co-administration of a cathartic enhances the elimination of phenobarbital and slow-release theophylline.[2] In theory, the risks of small bowel obstruction and constipation are decreased with administration of a cathartic.[2] Generally, concurrent use of cathartics with MDAC is not advised, especially in children, due to the potential to cause fluid

and electrolyte imbalance.[2] If cathartics are used, administration should be limited to one or two doses in 24 hours.[15]

Another challenge to address with administration of activated charcoal is patient compliance. In 2008, a prospective study of clinical trial patients was published, documenting compliance rates for SDAC and MDAC.[16] 599 patients were allocated for SDAC administration, and 544 for MDAC administration (6 doses). 88 patients did not complete the course, and 98 required and NG tube, which left 885 patients taking charcoal orally. 83% of those patients took charcoal orally as a single or first dose, and for MDAC patients, only 66% finished the 6-dose course. For the first dose, 3.2% of patients refused, and 12.3% refused the last dose. Among patients who received the sixth dose, 38% required "intense persuasion."[16] This study highlights the difficulty associated with patient compliance in the setting of MDAC, potentially further limiting efficacy if adequate doses are not obtained.

Adverse Effects

MDAC is typically well tolerated.[2] Most commonly reported side effects are nausea/vomiting, black stool, and mild constipation. More severe side effects include bowel obstruction, respiratory complications, and fluid/electrolyte abnormalities.[2] Dorrington et al. (2003) report a study of 878 patients who received MDAC between 1993 and 1998 in 4 North American cities and conclude that clinically significant complications from MDAC occur infrequently (1.6%).[17] A critique of this study states that MDAC was only appropriate in 7% of the patients, and that the study showed that charcoal is "inappropriately overused".[18]

Several reports of bowel obstruction have been reported, most often in patients who had underlying intestinal abnormalities.[2] One case was reported in 1994 where a patient with theophylline toxicity developed a small-bowel obstruction after MDAC (350 g total).[19] Patients

who have had a recent bowel surgery, rectal ulcers, or intestinal perforations may not be candidates for MDAC due to gastrointestinal complications.

The major respiratory complications associated with MDAC are aspiration pneumonia and airway obstruction.[2] Dorrington et al. (2003) report aspiration in 5 patients out of 878 who received MDAC.[17] In 1993, a case report was published where a male 30 years of age was hospitalized for a TCA overdose, and received multiple-dose activated charcoal.[20] In between doses, he pulled his NG tube out of position. When reinserted, it was unintentionally inserted into his lung, and the next dose was administered into the lung. The patient required bronchoscopic removal of charcoal from the lung, but improved with supportive care.[20]

Fluid, electrolyte, and acid-base abnormalities are most frequently seen in children and infants, and include hypernatremia, hypokalemia, hypermagnesemia, and metabolic acidosis.[2] Hypernatremia in particular is highly associated with the use of cathartics.[15]

Summary

Activated charcoal works by adsorbing xenobiotics and poisons to prevent systemic absorption (SDAC and MDAC) or enhance elimination (MDAC). MDAC has been shown to increase elimination or limit absorption for a number of xenobiotics, but generally has not been proven to improve clinical outcomes.

Dosing of MDAC is often institution- and case-specific, but usually consists of two or more doses of activated charcoal. Cathartics are not recommended due to adverse effects, and patient compliance is an important consideration for administration. Significant potential adverse effects caused by MDAC include gastrointestinal, respiratory, and fluid, electrolyte, and acid-base complications.

Overall, multiple-dose activated charcoal was used and studied more frequently in past years, but this treatment is still used occasionally for management of poisonings. Though not every ingestion of studied xenobiotics may benefit from MDAC, there may be specific poisoning situations where MDAC can be used as an adjunct therapy to minimize effects from a poison exposure.

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