Title: Does a soft drink mixture improve tolerance of activated charcoal in an adult without affecting efficacy: A randomized controlled crossover study

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Background

Activated charcoal has become an established component of gastrointestinal decontamination in the poisoned patient.[1] While the exact methods vary by manufacturer, the basic production process involves pyrolysis of organic material followed by exposure to an oxidizing gas at high temperature.[2] This results in a compound with a very large surface area – 800-1200 m^2/g.[3] Charcoal as a compound has been around for thousands of years, being used for heating and cooking for thousands of years.[4] The compounds ability to adsorb chemicals gradually began to be known. In 1773 organic chemist Carl Wilhelm Scheele used charcoal to absorb gases. In 1830, a French pharmacist named Touery survived after swallowing a lethal dose of strychnine with charcoal to prove its ability to adsorb poisons.

The efficacy of charcoal, though historically debated, has become rather well established. It has become a staple in the management of the poisoned patient. Numerous studies have proven that activated charcoal administration decreases the adsorption of xenobiotic from the gut in an overdose.[4-10] These have been done in both volunteer subjects and in poisoned patients. In addition, some studies have gone beyond simply looking at pharmacokinetic data and have looked at clinical outcome data. Although a detailed review of the literature is beyond the scope of this background section, several studies will be briefly reviewed here. In a study by Christophersen et al, healthy volunteers were given a sub-toxic dose of acetaminophen.[5] They discovered that charcoal significantly reduced the amount of acetaminophen absorbed from the gut when given at both 1 hour post-ingestion and 2 hours post-ingestion. However, the reduction was less significant when charcoal was given 2 hours post-ingestion compared to one hour post-ingestion, emphasizing the need to administer charcoal as early as possible post-ingestion. Another study by Yeates and Thomas looked at healthy volunteers given a sub-toxic dose of acetaminophen with charcoal administered at 1, 2, or 4 hours post-ingestion. They found a significant reduction in absorption of acetaminophen when charcoal was given 1 or 2 hours post-ingestion, but not 4 hours.[6] A study by Isbister et al looked at patients after intentional ingestion of citalopram.[7] They found that charcoal those that received charcoal were less likely to experience a prolonged QT on EKG. Finally, a study by Underhill et al looked at patients presenting after an intentional ingestion of acetaminophen and randomized them to different methods of GI decontamination: gastric lavage, activated charcoal, ipecacuanha, or no decontamination. They found that activated charcoal was the most effective decontamination method.[8]

Despite the apparent benefit of activated charcoal, one of the main limitations to its use is its taste and appearance. As such, numerous studies have looked at different mixtures to try to improve the taste/appearance of the charcoal.[12-15] The results of these studies are mixed, but, for the most part, find that charcoal is better received if it is mixed in

something like cola or chocolate milk. However, the caveat is that some of these vehicles used to improve the palatability of the charcoal may decrease its ability to adsorb xenobiotic. Ice cream has been found to decrease the efficacy of the charcoal.[16] Jam has been found to not affect the efficacy of the charcoal.[17] Chocolate syrup has had mixed resulted.[18-19] Yogurt was found to not affect the efficacy of the charcoal in vivo but did affect the efficacy in vitro.[15]

Despite several taste test studies looking at the effects of cola in improvement in palatability of charcoal, there does not appear to be any studies looking to see if cola affects the efficacy of charcoal. This is likely the most likely mixture in the Emergency Department as soft drinks are readily available in the patient nourishment supplies.

In addition, there are no studies to our knowledge looking at comparison between clear and opaque containers in charcoal tolerance. There also are not any randomized controlled trials in poisoned patients. This study will be a pilot study to demonstrate that mixing charcoal with cola does not affect the efficacy of the charcoal, allowing us to continue on to the randomized controlled trial.

References

1. Smith SW, Howland M. Activated Charcoal. In: Nelson LS, Howland M, Lewin NA, Smith SW, Goldfrank LR, Hoffman RS. Eds. Goldfrank's Toxicologic Emergencies, 11e New York, NY: McGraw-Hill.

2. Paddock Laboratories LRLPC. Actidose-Aqua & Actidose ® with Sorbitol. Actidose ® with Sorbitol. Actidose ®-Aqua. Activated Charcoal Suspension [product label]. Minneapolis, MN: Paddock Laboratories, LLC; 2014.

3. Olson KR. Activated Charcoal for acute poisoning: one toxicologist's journey. J Med Toxicol. 2010;6:190-198.

4. Olson KR. Activated charcoal for acute poisoning: one toxicologist's journey. J Med Toxicol. 2010; 6:190-198.

5. Marketos SG, Androutsos G. Charcoal: from antiquity to artificial kidney. J Nephrol. 2004;17:453-456.

6. Christophersen AB, Levin D, Hoegberg LCG, Angelo HR, Kampmann JP. Activated charcoal alone or after gastric lavage: a simulated large paracetamol intoxication. Br J Clin Pharmacol. 2002;53:312-317

7. Yeates PJA and Thomas SHL. Effectiveness of delayed activated charcoal administration in simulated paracetamol (acetaminophen) overdose. Br J Clin Pharmacol. 2000;49:1-14.

8. Isblster GK, Friberg LE, Stokes B, Buckley NA, Lee C, Gunja N, Brown SG, MacDonald E, Graudlins A, Holdgate A, Duffull SB. Activated charcoal decreases the risk of

QT prolongation after citalopram overdose. Annals of Emergency Medicine. 2007;50(5):593-600.
9. Underhill TJ, Greene MK, Dove AF. A comparison of the efficacy of gastric lavage, ipecacuanha, and activated charcoal in the emergency management of paracetamol overdose. Archives of Emergency Medicine. 1990. 7:148-154.
10. Buckley NA, Whyte IM, O'Connell DL, Dawson AH. Activated charcoal reduces the need for N-acetylcysteine treatment after acetaminophen (paracetamol) overdose. Clinical Toxicology 1999;37(6):753-757.
11. Friberg LE, Isbister GK, Duffull SB. Pharmacokinetic-pharmacodynamic modelling of QT interval prolongation following citalopram overdoses. Br J Clin Pharmacol. 2005;61(2):177-190.
12. Cheng A, Ratnapalan S. Improving the palatability of activated charcoal in pediatric patients. Pediatric Emergency Care. 2007;23(6):384-386.
13. Dagnone D, Matsui D, Rieder MJ. Assessment of the palatability of vehicles for activated charcoal in pediatric volunteers. Pediatric Emergency Care. 2002;18(1):19-21.
14. Skokan EG, Junkins EP, Corneli HM. Taste test: children rate flavoring agents used with activated charcoal. Arch Pediatr Adolesc Med. 2001;155(6):683-686.
15. Hoegberg LCG, Christophersen AB, Christensen HR, Angelo HR. Comparison of the adsorption capacities of an activated-charcoal-yogurt mixture versus activated-charcoal-water slurry in vivo and in vitro. Clinical Toxicology. 2005;43:269-275.
16. Levy G, Soda DM, Lampman TA. Inhibition by ice cream of the antidotal efficacy of activated charcoal. Amer J Hosp Pharm. 1975;32:289-291.
17. Neve, RE. Antidotal efficacy of activated charcoal in presence of jam, startch, and milk. Am J Hosp Pharm. 1976;33:965-966.
18. Scholtz EC, Jaffe JM, Colaizzi JL. Evaluation of five activated charcoal formulations for inhibition of aspirin absorption and palatability in man. Am J Hosp Pharm. 1978;35:1355-1359.
19. Navarro KR, Krenzelok EP. Relative efficacy and palatability of three activated charcoal mixtures. Veterinary and human toxicology. 1980;22(1):6-9.

Protocol:

Recruitment: 5 subjects will be recruited through flyers and word of mouth.

Inclusion: Healthy non-pregnant adults ages 18-40

Exclusion:

- Self-reported history of any hepatic, gastrointestinal, or renal disease.

- Self-reported history of alcohol or drug abuse (defined as any use of illicit drugs, alcohol use greater than the CDC standard recommended amount of 2 drinks per day in men).
- Any current daily prescription medication use
- Any allergy to Tylenol
- Pregnant women
- Age <18 or >40
- Any gluten allergy or intolerance
- Weight <60 kg or >93 kg
- Prisoners
- Adults unable to consent

Participants will be provided the inclusion and exclusion criteria when they contact an investigator about the study. Inclusion/exclusion criteria are confirmed and documented at each protocol visit. We will use a screening questionnaire to access potential subjects based on the inclusion/exclusion criteria

Settings

The Clinical Research Unit in the Institute for Human Performance will be used to conduct the study. For screening, discussion of private information will be performed over the phone from a private office in the Poison Control Center.

Study Day Method/Procedure:

Visit 1

a. This will be done over the phone from a private office in the Poison Control Center
b. Will review inclusion/exclusion criteria to look at eligibility
c. If done in person, will obtain signed consent

The following will be collected at the start of visit 2

a. Age
b. Weight measured

Visit 2 and 3

a. If not already signed on visit 1, consent forms will be signed before initiation of the study

b. *Participants will be told in advance not to consume any alcohol the day before, day of, or day after the experiment*
c. *Women will complete a pregnancy test on arrival to ensure exclusion criteria are not met.*
d. *Participants will be told in advance not use consume and products containing acetaminophen the 5 days before, day of, and 5 days after the experiment*
e. *Participants arrive at 8 AM after an overnight fast to have commenced at 4am. They will have refrained from using acetaminophen for 5 days prior to the study.*
f. *Participants will have their age and weight measured.*
g. *Subjects will be fed a light breakfast of 2 pieces of dry toast and 200 mL of water*
h. *A peripheral IV will be placed in the antecubital fossa for blood draws*
    i. *Area will be cleaned with an alcohol wipe*
    ii. *Tourniquet will be placed on the arm proximal to planned IV insertion site*
    iii. *IV tubing will be prepped with a saline flush*
    iv. *Vein will be accessed with an angiocath IV catheter (needle size determined by the nurse)*
    v. *Prepped IV tubing will be connected to the catheter and the line will be secured to the skin with a tegaderm.*
i. *Acetaminophen ingestion will occur 1 hour after completion of the breakfast*
    i. *45 mg/kg acetaminophen will be administered with 150 mL of water. The number of tablets will be rounded down to the nearest whole number*
    ii. *325 mg tablets will be utilized to increase the gut burden of tablets to more closely mimic the overdose setting. The number of tablets will be rounded down to the nearest whole number*
    iii. *A max weight of 93 kg will be set for the participants. With this max weight, a participant at the max weight of 93 kg would be expected to ingest 4185 mg of Tylenol. However, as we are rounding down to the nearest tablet, they would only ingest 3,900 mg of Tylenol, below the 4g recommended daily limit.*
j. *Subjects will consume the charcoal mixture 1 hour after consumption of the acetaminophen tablets. Using a random number generator, participants will be assigned to either the control charcoal of the soda-charcoal mix for the first experimental day.*

i. *For the control day, 50 g activated charcoal will be administered by itself. Actidose-aqua, a pre-mixed charcoal-water slurry, will be used*

ii. *For the study day, 50 g activated charcoal (Actidose-aqua) will be administered as a mixture with 240 cc soft drink (1:1 charcoal to soft drink). Actidose-aqua will be used*

k. *Subjects will rate the appearance, smell, flavor, texture, and overall appeal of the charcoal mixture on a 1-10 scale, 10 being the best and 1 being the worst.*

l. *Blood for acetaminophen assay will be drawn in a Gold or Mint tube (approximately 5 mL per tube) at 0, 15, 30, 45, 60, 75, 90, 120, 180, 240, minutes*

i. *Samples will be taken to the lab for processing*

ii. *Samples will be run using Abbott's Acetaminophen L3K assays (enzymatic colometric assay)*

m. *Subjects will receive a light snack of crackers and water no sooner than 3 hours after the charcoal is consumed (4 hours after acetaminophen was ingested).*

n. *Participants will be reminded to refrain from using acetaminophen for 5 days after the study*

Statistical Analysis

Differences in all measures on the palatability questionnaire will be analyzed using a paired sample t-test with 95% confidence intervals.

To analyze differences in the pharmacokinetics between the study arms, the area under the curve, time of maximum concentration, and maximum concentration will be obtained. Area under the curve is used as a marker of drug absorption and will be calculated utilizing the trapezoidal rule. A paired t-test will be performed for comparison with 95% confidence intervals.

To compare the mg/kg dosing of acetaminophen for each arm of the study, a paired sample t-test will be performed.

All analysis will be conducted using IBM SPSS Version 26. The level of significance was set at a p-value <0.05.