Drug Adsorption Efficacy and Palatability of a Novel Charcoal Cookie Formulation

Wendy Klein-Schwartz, Pharm.D., M.P.H., Suzanne Doyon, M.D., FACMT, and Thomas Dowling, Pharm.D., Ph.D., FCP

Study Objectives. To determine the effect of a novel charcoal cookie formulation compared with a standard aqueous charcoal product on the absorption of orally administered cimetidine, and to compare the palatability of the two charcoal products.

Design. Prospective, open-label, three-way, crossover trial.

Setting. General clinical research center.

Subjects. Eight healthy volunteers (five men, three women; mean age 23.4 yrs).

Intervention. After an overnight fast, each subject ingested a single cimetidine 800-mg tablet. Fifteen minutes later, subjects were randomly assigned to receive either water (control), three charcoal cookies (equivalent to 7.2 g of charcoal), or 7.2 g of aqueous activated charcoal suspension. Subjects then received each of the other study treatments—cimetidine with water, cimetidine with charcoal cookies, and cimetidine with charcoal suspension—separated by a 1-week washout period between each treatment.

Measurements and Main Results. Venous blood samples were obtained before and 8 hours after administration of the cimetidine dose. Noncompartmental pharmacokinetic analysis was performed, and area under the plasma concentration–time curve (AUC) and maximum plasma concentration ($C_{\text{max}}$) were compared for each study drug combination. In addition, subjects evaluated the palatability of each charcoal product by using a visual analog scale. Both charcoal products effectively adsorbed cimetidine, resulting in decreased absorption of most of the cimetidine dose. No significant difference was noted in the median percent decrease in cimetidine AUC between the charcoal suspension and charcoal cookie (91.8% vs 82.1%, p=0.505). Similarly, no significant difference was noted in the median percent decrease in $C_{\text{max}}$ between the two charcoal formulations (82.6% vs 64.0%, p=0.574). The palatability scores, however, were significantly higher for the charcoal cookie than for the charcoal suspension. All study drugs were well tolerated, and no adverse events were reported.

Conclusion. The new charcoal cookie formulation appears to be as effective as the aqueous charcoal suspension at reducing absorption of cimetidine. In addition, the charcoal cookie was rated as more palatable than the aqueous charcoal suspension, suggesting that the charcoal cookie could be an attractive alternative to the charcoal slurry for managing drug overdoses.

Key Words: activated charcoal, poisoning, gastrointestinal decontamination, toxicology.

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ingested substance. The aqueous preparation of activated charcoal is usually administered enterally, either by oral administration or through a nasogastric or orogastric tube, after the ingestion of a toxic amount of poison. Aqueous activated charcoal is unappealing in appearance (black suspended particles) and bland tasting with a gritty texture.

Pediatric poisonings are usually unintentional, involve small quantities of substances, and can be managed at home. The American Academy of Pediatrics and other organizations have been reticent, however, to recommend the use of activated charcoal in the home, in part because of a lack of data, and in part related to concerns that parents will be unable to convince children to drink a therapeutic dose due to the agent’s poor palatability.

A pleasant-tasting, appealing, and easy-to-administer activated charcoal product is needed. A wafer cookie (De Novo, Inc., Baltimore, MD) containing 2.3 g of activated charcoal (United States Pharmacopeia) as the only active ingredient has been formulated. In vitro studies comparing the charcoal cookie with an aqueous charcoal suspension (Actidose-Aqua; Paddock Laboratories, Inc., Minneapolis, MN) with use of sodium salicylate as the test drug have shown essentially identical adsorptive capacities (personal communication, M. Stang, M.D., De Novo, Inc., November 19, 2008 [written copy of submission to United States Food and Drug Administration (FDA), Division of Dockets Management, Docket No. 1981N-0050]). However, clinical studies are needed to confirm the findings. If the charcoal cookie demonstrates a high adsorptive capacity similar to the aqueous slurry and is deemed more palatable, then poison management in homes may increase.

The objective of this study was to quantify the adsorptive capacity of the charcoal cookie compared with a standard aqueous activated charcoal preparation, as measured by differences in relative percentage absorption of cimetidine. A secondary objective was to assess the palatability of the charcoal cookie compared with the aqueous charcoal product.

Methods

Study Design and Subjects

This study, conducted at the University of Maryland’s General Clinical Research Center (GCRC), was a prospective, open-label, three-way crossover trial in which healthy volunteers served as their own controls. Healthy volunteers aged 18–35 years were recruited by fliers placed at various locations on the University of Maryland Baltimore campus. Exclusion criteria were diabetes mellitus, gastrointestinal disease (gastroesophageal reflux disease, inflammatory bowel disease, irritable bowel syndrome, peptic ulcer disease), hepatic or renal disease, or any other medical condition considered significant by the physician. Subjects were also excluded from participating in the study if they had excessive alcohol use (defined as current alcohol consumption ≥ 2 drinks/day), were taking a drug known to interact with cimetidine, or had a known allergy to chocolate, vanilla, or cimetidine. Female subjects were excluded if they were pregnant or not using oral contraceptive birth control.

The study was conducted according to Good Clinical Practice procedures, and all study events were documented by GCRC research personnel. The study was approved by the University of Maryland Institutional Review Board and the GCRC Advisory Committee. All study subjects provided written informed consent before participating in the study.

Study Drugs

The charcoal cookies were manufactured under Good Manufacturing Practices guidelines. The cookies were prepared by using activated charcoal (PICA Medicinal 50; PICA, Columbus, OH) and FDA-approved food ingredients such as corn starch, glycerin, and sweeteners. They were baked at 325°F, cooled, and packaged. The other study drugs, aqueous charcoal suspension (Actidose-Aqua; Paddock Laboratories, Inc.) and cimetidine (IVAX Pharmaceuticals, Inc., Miami, FL), were commercially available products. Cimetidine was chosen as the absorption marker...
in this study because of its low adverse-effect profile as well as human volunteer data demonstrating that it is adsorbed by activated charcoal. All study drugs were dispensed by the investigational drug service at the GCRC.

Randomization

With use of the Research Randomizer program (www.randomizer.org), eight sets of three numbers (1, 2, and 3) per set were generated. As each subject was entered into the study, he or she was assigned to the next consecutive set of numbers, which determined the order in which the subject received each study drug combination: cimetidine alone (1 [control]), cimetidine with charcoal cookies (2), and cimetidine with aqueous charcoal suspension (3).

Study Procedures

After an overnight fast of at least 12 hours, subjects were admitted to the GCRC for placement of a peripheral venous catheter for blood sampling. A standard normal saline flush was used to keep the catheter patent. Each subject ingested a single cimetidine 800-mg tablet with up to 90 ml of water. Fifteen minutes later, subjects were randomly assigned to receive either 180 ml of water (control), three charcoal cookies (equivalent to 7.2 g of charcoal) with 180 ml of water, or 35 ml of aqueous charcoal suspension (7.2 g of charcoal) plus 145 ml of water. Subjects were allowed up to 5 minutes to consume the study drugs. The doses of charcoal were based on a standard charcoal:drug ratio of approximately 10:1. Subjects continued to fast for 2 more hours, after which a light snack of a carbonated beverage and plain crackers was offered.

Immediately after receiving the charcoal cookies or suspension, the study subjects were asked to evaluate the palatability of the charcoal by using a 4.25-inch, modified, facial-hedonic visual analog scale. Subjects marked an X on the line below a 5-point face scale (pictures of five faces ranging from frowning to neutral to smiling) to demonstrate their opinion of the product’s taste. Subjects also were given a form to document any adverse events that occurred after discharge from the GCRC. The form included a table to document any adverse effects, including when the adverse effect started and stopped, the illness or symptoms, severity, and treatment. Subjects were provided with a severity scale that defined mild (easily tolerated), moderate (some interference with activity), severe (prevents daily activity, requires medical treatment), and potentially life-threatening (emergency department visit or hospitalization).

Each subject visited the GCRC 2 more times to receive the other two study treatments. Each visit was separated by at least a 1-week washout period.

Pharmacokinetic Sampling and Analytic Methods

At each visit, venous blood samples of approximately 4 ml were obtained before the cimetidine dose (baseline) and 0.5, 1, 1.5, 2, 3, 4, 6, and 8 hours after the cimetidine dose. After immediate centrifugation, the plasma was harvested and frozen at −20°C until analysis.

Cimetidine plasma concentrations were determined by high-performance liquid chromatography (HPLC) with use of a method that was developed and validated in our laboratory. Briefly, plasma samples of 0.25 ml were alkalinized followed by liquid-liquid extraction with water-saturated ethyl acetate, then evaporated under nitrogen. The extracts were reconstituted in mobile phase (0.1 ml) and injected onto a C18 reversed-phase column (Prodigy 5-µ ODS3, C18, 4.6 mm x 250 mm; Phenomenex, Inc., Torrance, CA). The HPLC system consisted of a Waters 2690 separation module (Waters Millipore; Waters Corp., Milford, MA), and a model 2487 dual wavelength absorbance detector set at 228 nm. The mobile phase consisted of acetonitrile and heptanesulfonic acid 2.5 g/L in an aqueous 20-mM sodium acetate buffer (23:77) at isocratic flow rate of 1.0 ml/minute. The standard curves were linear over the range of 0.025–4.0 mg/L (r²=0.995); within- and between-day coefficients of variation were both 5.2% or less.

Pharmacokinetic Assessments

Pharmacokinetic analysis of the plasma concentration data was performed by using noncompartmental methods in WinNonlin, version 3.1 (Pharsight Corp., Mountain View, CA). The peak plasma cimetidine concentration (Cmax) and the time to Cmax were determined from the observed plasma concentration–time data. The area under the plasma cimetidine concentration–time curve (AUC) from 0–480 minutes was calculated by using the linear trapezoidal method. Cimetidine pharmacokinetic parameter estimates were summarized with respect to treatment phase: cimetidine alone (control), cimetidine with charcoal cookies, or cimetidine with aqueous charcoal suspension.
Statistical Analysis

The target sample size of eight subjects was based on an α of 0.05, β of 0.20, and an expected difference of at least 40% in AUC and C_max for the control and charcoal preparations.

Statistics were performed by using SigmaStat, version 3.1 (Systat Software, Inc., Richmond, CA). Median and interquartile ranges (IQRs) were determined for AUC and C_max. Comparisons of median cimetidine AUC and C_max values across treatment phases were performed by using the Mann-Whitney rank sum test. The palatability data were analyzed with a paired t test by comparing the inches on the visual analog scale for the two charcoal products. For all tests, a p value of 0.05 or less was considered to indicate a statistically significant difference.

Results

Eight healthy volunteers (five men, three women; mean ± SD age 23.4 ± 5.32 yrs, range 19–35 yrs) completed the study between June and September 2009 (Table 1). One additional subject withdrew from the study due to an unrelated medical condition after completing one arm of the study; that subject’s data were not included in our results.

Both charcoal products effectively adsorbed cimetidine, resulting in decreased absorption of 89.7% of the cimetidine dose (Figures 1 and 2, and Table 2). No statistically significant difference was noted in median percent decrease in cimetidine AUC between the charcoal suspension and charcoal cookies (91.8% vs 82.1%, p=0.505). Similarly, no significant difference was noted in the median percent decrease in C_max between the charcoal suspension and charcoal cookies (82.6% vs 64.0%, p=0.574).

The findings in one participant (subject no. 4) were atypical. The AUC for cimetidine was higher after the aqueous charcoal suspension when compared with cimetidine alone. When removing this outlier, the median percent decrease in cimetidine AUC for the charcoal suspension and charcoal cookie was 93.2% (IQR −95.1% to −89.3%) and 82.7% (IQR −91.2% to −75.4%), respectively (p=0.383). The median percent decrease in C_max for the charcoal suspension and charcoal cookies changed to 84.1% (IQR −89.6% to −60.2%) and 70.5% (IQR −81.0% to −48.8%), respectively (p=0.456).

Subjects uniformly rated the palatability of the charcoal cookie higher than that of the charcoal suspension. Palatability taste scores were available for seven subjects; the charcoal cookie visual analog scale score was inadvertently not recorded by one subject. The mean ± SD score was 2.32 ± 0.83 for the charcoal cookie versus 1.08 ± 0.70 for the charcoal suspension (p=0.001).

No subject vomited the charcoal, and no adverse events were reported.

Discussion

To our knowledge, this is the first clinical trial that shows that a charcoal cookie effectively adsorbs a drug substance (cimetidine) similar to an aqueous charcoal slurry. The cookie reduced cimetidine AUC and C_max by approximately 82% and 64%, respectively. We found no significant difference in the relative efficacy of the charcoal cookie and aqueous charcoal slurry, which is the only comparative product available. The aqueous charcoal is known to adsorb various drugs and other compounds, preventing or minimizing absorption into the systemic circulation. Human volunteer studies demonstrated that activated

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**Table 1. Baseline Demographics of the Eight Volunteers**

<table>
<thead>
<tr>
<th>Subject No.</th>
<th>Age (yrs)</th>
<th>Race-Ethnicity</th>
<th>Weight (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>22/F</td>
<td>Hispanic</td>
<td>50.5</td>
</tr>
<tr>
<td>2</td>
<td>19/M</td>
<td>Caucasian</td>
<td>61.4</td>
</tr>
<tr>
<td>3</td>
<td>20/M</td>
<td>African-American</td>
<td>66.4</td>
</tr>
<tr>
<td>4</td>
<td>23/M</td>
<td>Hispanic</td>
<td>71.2</td>
</tr>
<tr>
<td>5</td>
<td>21/F</td>
<td>Caucasian</td>
<td>117.7</td>
</tr>
<tr>
<td>6</td>
<td>20/F</td>
<td>Caucasian</td>
<td>87.3</td>
</tr>
<tr>
<td>7</td>
<td>27/M</td>
<td>Caucasian</td>
<td>82.7</td>
</tr>
<tr>
<td>8</td>
<td>35/M</td>
<td>African-American</td>
<td>102.3</td>
</tr>
</tbody>
</table>

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Figure 1. Plasma cimetidine concentrations during the study treatment in the eight healthy volunteers. Both charcoal products effectively adsorbed cimetidine, resulting in decreased absorption of 89.7% of the cimetidine dose.
charcoal is most beneficial if administered within 1 hour of drug ingestion. In 40 studies involving volunteers, administration of 50 g or more of activated charcoal within 30 minutes of drug administration resulted in a mean reduction of bioavailability of 47%. Extending the interval between drug and activated charcoal to 60 minutes and 120 minutes reduced bioavailability to 40% and 16%, respectively. Our finding of markedly decreased cimetidine absorption when either the charcoal slurry or cookie was administered 15 minutes after the cimetidine dose is consistent with the results of these studies.

We describe unusual pharmacokinetic findings in one subject (subject no. 4). This subject appeared to absorb more cimetidine with the charcoal slurry than with cimetidine alone. This same subject experienced a decrease in cimetidine absorption when the charcoal slurry was administered 15 minutes after the cimetidine dose.

Table 2. Pharmacokinetics of Cimetidine Alone and After Oral Administration of the Charcoal Preparations

<table>
<thead>
<tr>
<th>Subject No.</th>
<th>Charcoal Suspension</th>
<th>Charcoal Cookie</th>
<th>Cimetidine Alone</th>
<th>Charcoal Suspension</th>
<th>Charcoal Cookie</th>
<th>Cimetidine Alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.74 (−95.4%)</td>
<td>4.32 (−73.3%)</td>
<td>16.21</td>
<td>0.30 (−92.2%)</td>
<td>2.08 (−45.8%)</td>
<td>3.84</td>
</tr>
<tr>
<td>2</td>
<td>1.30 (−90.5%)</td>
<td>1.20 (−91.2%)</td>
<td>13.68</td>
<td>0.62 (−81.0%)</td>
<td>0.55 (−83.2%)</td>
<td>3.27</td>
</tr>
<tr>
<td>3</td>
<td>8.62 (−35.4%)</td>
<td>2.47 (−81.5%)</td>
<td>13.36</td>
<td>2.39 (−9.4%)</td>
<td>0.78 (−70.5%)</td>
<td>2.64</td>
</tr>
<tr>
<td>4</td>
<td>8.17 (12.6%)</td>
<td>3.31 (−26.9%)</td>
<td>7.26</td>
<td>3.43 (64.7%)</td>
<td>2.20 (5.9%)</td>
<td>2.08</td>
</tr>
<tr>
<td>5</td>
<td>0.81 (−93.2%)</td>
<td>0.33 (−97.2%)</td>
<td>11.90</td>
<td>0.39 (−89.4%)</td>
<td>0.11 (−97.1%)</td>
<td>3.68</td>
</tr>
<tr>
<td>6</td>
<td>0.40 (−94.0%)</td>
<td>0.59 (−91.2%)</td>
<td>6.73</td>
<td>0.29 (−84.1%)</td>
<td>0.46 (−74.6%)</td>
<td>1.83</td>
</tr>
<tr>
<td>7</td>
<td>1.22 (−88.9%)</td>
<td>1.91 (−82.7%)</td>
<td>11.08</td>
<td>1.08 (−53.2%)</td>
<td>0.98 (−57.6%)</td>
<td>2.30</td>
</tr>
<tr>
<td>8</td>
<td>0.24 (−95.9%)</td>
<td>1.87 (−67.8%)</td>
<td>5.82</td>
<td>0.14 (−89.7%)</td>
<td>0.84 (−37.5%)</td>
<td>1.34</td>
</tr>
<tr>
<td>Median</td>
<td>1.02 (−91.8%)</td>
<td>1.89 (−82.1%)</td>
<td>11.49</td>
<td>0.51 (−82.6%)</td>
<td>0.81 (−64.0%)</td>
<td>2.47</td>
</tr>
<tr>
<td>IQR</td>
<td>0.57–4.74</td>
<td>0.90–3.40</td>
<td>(7.0–13.52)</td>
<td>0.30–1.74</td>
<td>0.50–1.53</td>
<td>2.00–3.48</td>
</tr>
</tbody>
</table>

Data in parentheses are percent differences from cimetidine alone (control).

AUC = area under the plasma concentration–time curve; Cmax = maximum plasma concentration; IQR = interquartile range.

*p<0.01 vs cimetidine alone (control).

bp<0.05 vs cimetidine alone (control).

Figure 2. Effect of charcoal preparations on the cimetidine (A) area under the plasma concentration–time curve (AUC) and (B) maximum plasma concentration (Cmax). No statistically significant difference was noted in median percent decrease in cimetidine AUC or Cmax between the charcoal suspension and charcoal cookies. Data are median (interquartile range). *p<0.01 versus control.
absorption after the charcoal cookie, but not to the extent demonstrated by the other subjects. It is conceivable that this subject absorbed cimetidine so rapidly that the administration of charcoal 15 minutes after the cimetidine dose did not reduce cimetidine absorption. Data analysis performed with and without this outlier showed similar findings.

Early administration of activated charcoal maximizes reduction in toxin absorption. For adults who overdose and require treatment in a health care facility, the time interval between ingestion and arrival in the emergency department is usually over 1 hour. Treatment is further delayed due to triage and assessment by medical staff in the emergency department. A study of prehospital use of activated charcoal found that patients received the product in the ambulance an average of 46 minutes earlier than patients who received it in the emergency department. Availability of a product that can be easily administered in the prehospital setting could be beneficial. The charcoal cookie may have a role in this setting in the early-presenting awake patient who can chew and swallow cookies.

Both the aqueous charcoal suspension product and the charcoal cookie were well tolerated, although subjects uniformly scored the palatability of the charcoal cookie higher than the aqueous slurry. Activated charcoal has a potential role in the management of childhood poisoning in the home. However, poor palatability of the aqueous charcoal slurry raises concerns regarding its utility in this setting. Two studies found that children did not drink a full dose of activated charcoal when administered in the home or a simulated home environment. A third study found that children ingested an adequate dose (mean 12.1 g) and that home use reduced time to charcoal administration compared with its administration in the emergency department.

There is a need for a pleasant-tasting and appealing activated charcoal product. The charcoal cookie may meet this need and increase compliance with home administration.

Children and adults have been used to assess palatability of products intended for children. The visual analog scale is a tool for measuring subjective characteristics in which participants show their level of agreement by choosing a position along a continuous line anchored by words (e.g., good...bad; no pain...worse pain) or associated with pictures (e.g., frowning faces...smiling faces). Uses for this scale include assessment of pain and of appetite sensations (e.g., visual appeal, smell, taste, palatability). Examples of visual analog scales to assess the palatability of flavoring vehicles for activated charcoal include a 10-point faces scale and a modified facial-hedonic (5 faces) scale. The latter scale was selected for this study because of its simplicity. Studies of flavoring vehicles in pediatric volunteers have found that addition of a cola drink or cherry-flavored syrup improves charcoal palatability for children. However, adding flavoring agents to the activated charcoal slurry is discouraged since these substances may decrease the adsorptive capacity of the charcoal. Our study evaluated the efficacy (i.e., adsorptive capacity) of a charcoal cookie formulation to reduce cimetidine absorption and compared its palatability with that of a commonly used aqueous charcoal preparation. By using the modified facial-hedonic scale in adult subjects, the charcoal cookie was judged as more palatable than the charcoal slurry, without compromising the charcoal's adsorptive capacity.

Our study has limitations. First, subjects were fasting and received a therapeutic dose of cimetidine; therefore, the results may not be generalizable to patients with overdoses. With the larger doses of activated charcoal required to manage overdose, it is unknown whether the preference for the charcoal cookie would persist if more cookies needed to be ingested. The charcoal product was administered at 15 minutes after the cimetidine dose. Although this time frame is not feasible for most cases of overdose in adults who are treated in the emergency department, it may be a reasonable time interval for use of charcoal in the home or by prehospital providers. Finally, preference for the cookie over the charcoal slurry in adults may not be generalizable to children.

Conclusion

A novel charcoal cookie formulation appears to be as effective as aqueous charcoal suspension at reducing absorption of cimetidine. The charcoal cookie was also more palatable than the aqueous charcoal suspension, suggesting that the charcoal cookie could be an attractive alternative to the charcoal slurry for managing overdoses.

Acknowledgment

We thank Michael Stang, M.D., DeNovo, Inc., for supplying the charcoal cookies.
References