

Evaluation of a Novel Charcoal Cookie Formulation for Drug Adsorption

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Key words: activated charcoal, poisoning, gastrointestinal decontamination, toxicology

Running head: Novel charcoal cookie

The research was funded by an award from the Frontiers Fund Research Institute of the American College of Clinical Pharmacy. This work was supported by the University of Maryland General Clinical Research Center Grant M01 RR 16500, General Clinical Research Centers Program, National Center for Research Resources (NCRR), NIH.

Abstract

Study Objectives: To determine the relative effect of a new charcoal cookie formulation on the absorption of orally administered cimetidine compared to a standard aqueous charcoal product; to compare the relative palatability of the two products.

Design: Prospective, open-label, three-way cross-over trial

Setting: General Clinical Research Center at University of Maryland Medical Center

Patients: 8 healthy volunteers (ages 18 to 35 years of age).

Intervention: After an overnight fast, subjects ingested cimetidine 800 mg tablet. At 15 minutes after the cimetidine dose subjects ingested either water, 3 charcoal cookies (equivalent to 7.2 g charcoal) or 7.2 g of aqueous activated charcoal suspension.

Measurements: Venous blood samples were obtained over an 8 hour period for noncompartmental pharmacokinetic analysis including AUC and C_{max}. Subjects evaluated the palatability of each product using a visual analog scale (VAS).

Main Results: Both charcoal products effectively adsorbed cimetidine resulting in decreased absorption of most of the cimetidine dose. There was no difference in median percent decrease in cimetidine AUC (mg*hr/L) for the charcoal suspension and charcoal cookie [91.8% vs 82.1%] (p=0.505). Similarly, there was no difference in the median percent decrease in C_{max} (mg/L) for the charcoal suspension and charcoal cookies [82.6% vs 64.0%] (p=0.574). The palatability taste scores on VAS were 2.32 ±0.83 for the charcoal cookie and 1.08 ± 0.70 for the charcoal suspension. There was a significant difference in the palatability scores (p=0.001). All products were well tolerated and there were no adverse events reported.

Conclusions: A new charcoal cookie formulation is as effective as the aqueous charcoal suspension at reducing absorption of cimetidine. The charcoal cookie is more palatable than the aqueous charcoal suspension.

Introduction

Single dose activated charcoal is the primary method of gastrointestinal decontamination for the management of poisonings.¹ It is the most effective method of preventing the systemic absorption of an ingested substance.² The aqueous preparation of activated charcoal is usually administered enterally, either by oral administration or via 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.³ As such, some pediatric poisonings can be managed at home and activated charcoal has a potential role in this setting. The American Academy of Pediatrics and others have been reticent to recommend the use of activated charcoal in the home, in part because of the lack of data, and in part related to concerns that parents will be unable to convince children to drink a therapeutic dose due to poor palatability.⁴⁻⁶

We perceive a need for a pleasant tasting appealing and easy to administer activated charcoal product. A wafer cookie (De Novo, Inc., Baltimore, MD) containing 2.3 g of activated charcoal USP as the only active ingredient has been formulated. In-vitro studies comparing the charcoal cookie with Actidose-Aqua® (Paddock Laboratories, Inc., Minneapolis, MN) using sodium salicylate as the test drug have shown essentially identical adsorptive capacities. (Personal Communication to Dr. Klein-Schwartz from Dr. Michael Stang, President, De Novo, Inc.; written copy of submission to FDA, Division of Dockets Management, Docket No. 1981N-0050, November 19, 2008). However, clinical studies are needed to confirm these findings. If the charcoal cookie demonstrates a high adsorptive capacity similar to the

aqueous slurry and is deemed more palatable, this novel charcoal product may increase compliance with home administration of activated charcoal in the management of poisoning.

The objective of this study is to quantify the adsorptive capacity of the charcoal cookie compared to a standard aqueous activated charcoal preparation as measured by differences in relative percent absorption of cimetidine. A secondary objective is to assess the palatability of the charcoal cookie compared with an aqueous charcoal product as measured on a visual analog scale.

Research Design and Methods

This study was a prospective, open-label three-way cross-over trial in which healthy volunteers served as their own controls, with a one week washout period. Eight healthy adult volunteers ages 18 to 35 years were recruited by fliers placed at various locations on the University of Maryland Baltimore campus. A sample size of 8 subjects was determined based on α of 0.05, β of 0.20, and an expected difference of at least 40% in area-under-the curve plasma cimetidine concentration time curve and peak plasma cimetidine concentrations for the control and charcoal preparations. Any subject reporting a history or presence of the following conditions as determined by the screening physician was excluded from participating in the study: medical disease considered to be significant; diabetes mellitus, gastrointestinal disease (gastroesophageal reflux disease, inflammatory bowel disease, irritable bowel syndrome; peptic ulcer disease), hepatic or renal disease; pregnant women or women not using birth control (i.e., oral contraceptives); excessive ethanol use (defined as current alcohol consumption ≥ 2 drinks/day); currently taking medication known to interact with cimetidine, or known allergy to chocolate, vanilla or cimetidine. The study was approved by the by the University of Maryland Institutional Review Board and the General Clinical Research Center (GCRC) Advisory Committee.

The charcoal cookies were manufactured under GMP (Good Manufacturing Practices) guidelines. The cookies were prepared using activated charcoal (PICA Medicinal 50) 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, Actidose-Aqua and cimetidine (IVAX Pharmaceuticals, Inc., Miami, FL), are commercially available products. Cimetidine was chosen as the absorption marker in this study due to its low adverse effect profile as well as human volunteer data demonstrating that it is adsorbed by activated charcoal.⁷ All study drugs were dispensed by the Investigational Drug Service.

Using a Research Randomizer (www.randomizer.org/) 8 sets of 3 unique numbers 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 of the three study periods (#1=control; #2=charcoal cookies; #3=Actidose Aqua). After an overnight fast (at least 12 hours), subjects were admitted to the GCRC with placement of a peripheral venous catheter for blood draws. A standard normal saline flush was used to keep the line open. At time zero, the subject ingested a single cimetidine 800 mg tablet and up to 90 mL of water. At 15 minutes after the cimetidine dose was ingested, the subject was randomized to receive either 180 mL of water (control), 3 charcoal cookies (7.2 g total) with 180 mL of water or 35 mL of Actidose Aqua (7.2 g) plus 145 mL of water. Subjects were allowed up to 5 minutes to consume these agents. There was a one week washout between study periods. The doses of charcoal were based on a standard charcoal to drug ratio of approximately 10 to 1.⁸ Subjects continued to fast for 2 hours after the test dose, after which time a light snack of a carbonated beverage and plain crackers was offered.

Venous blood (approximately 4 mL) samples were obtained at baseline (pre-dose) and 0.5, 1, 1.5, 2, 3, 4, 6 and 8 hours post cimetidine dosing. Following immediate centrifugation, plasma was harvested and frozen -20°C until analysis. Cimetidine concentrations in plasma were determined by HPLC using a method that was developed and validated in our laboratory.⁹ Briefly, plasma samples (0.25 mL) were alkalized 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 (Phenomenex Prodigy 5µ ODS3, C18, 4.6mm x 250 mm). The HPLC system consisted of a Waters 2690 separation module (Waters Millipore, Millford, 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 20mM sodium acetate buffer (23:77) at isocratic flow rate of 1.0 mL/min. The standard curves were linear over the range of 0.025 to 4.0 mg/L ($r^2=0.995$); within-day and between-day coefficients of variation were $\leq 5.2\%$.

The study was conducted according to Good Clinical Practice procedures, and all study events were documented by GCRC research personnel during the first 8 hours of the study. Subjects were given an adverse event report form to document any adverse events that occur following discharge from the GCRC. The form included a table to document any adverse effects including when adverse effect started and stopped, the illness or symptoms, severity and treatment. Subjects were provided with a severity scale which included mild (easily tolerated), moderate (some interference with activity), severe (prevents daily activity, requires medical treatment) and potentially life threatening (ED visit or hospitalization).

Immediately after each dose of charcoal the study subjects were asked to evaluate the palatability of the charcoal using a 4.25 inch modified facial-hedonic visual analog scale (VAS).¹⁰ Subjects marked an X on the line below a 5-point faces scale (pictures of 5 faces ranging from frowning to neutral to smiling).

Pharmacokinetic analysis of the plasma concentration data was performed using noncompartmental methods in WinNonlin (v.3.1, Pharsight Corp., Mountain View, CA). The maximum concentration in plasma (C_{max}) and the time to maximal concentration (T_{max}) was determined from the observed plasma concentration-versus-time data. The area under the plasma concentration-versus-time curve from zero to 480 minutes (AUC) was calculated using the linear trapezoidal method. Cimetidine pharmacokinetic parameter estimates were summarized with respect to treatment phase (control, cookie or aqueous charcoal).

Statistics were performed using SigmaStat 3.1 (v 3.1, Systat Software, Inc. Richmond, CA). Median and interquartile ranges (IQR) on the median were determined for AUC and C_{max} . Comparisons of median cimetidine AUC and C_{max} values across treatment phases were performed using Mann-Whitney Rank Sum test. The palatability data were analyzed using paired t-test comparing the inches on the VAS scale for the two charcoal products. For all tests, significance was defined as a p value of 0.05 or less.

Results

Eight healthy volunteers (ages 19-35 years; average 23.4 ± 5.32) completed the study (Table 1). Three women and 5 men participated. One additional subject dropped out of the study due to an unrelated medical condition after completing one arm of the study and is not included in the study results.

Both charcoal products effectively adsorbed cimetidine resulting in decreased absorption of 89.7% of the cimetidine dose. (Figures 1 & 2, Table 2) There was no statistically significant difference in median percent decrease in cimetidine AUC (mg*hr/L) for the charcoal suspension and charcoal cookies [91.8% vs 82.1%] ($p=0.505$). Similarly, there was no significant difference in the median percent decrease in Cmax (mg/L) for the charcoal suspension and charcoal cookies [82.6% vs 64.0%] ($p=0.574$).

The findings in one subject (#4) were atypical. The AUC for cimetidine was higher following the aqueous charcoal suspension when compared to cimetidine alone. When removing this outlier, the median percent decrease in cimetidine AUC for the charcoal suspension and charcoal cookie were 93.2% (IQR, -95.1, -89.3) vs 82.7 (IQR, -91.2, -75.4), respectively ($p=0.383$). The median percent decrease in Cmax (mg/L) for the charcoal suspension and charcoal cookies changed to 84.1% (IQR, -89.6, -60.2) and 70.5% (IQR, -81.0, -48.8), respectively ($p=0.456$).

Subjects uniformly rated the palatability of the charcoal cookie higher than the charcoal suspension. The palatability taste scores on the VAS were available for $n=7$ subjects with 2.32 ± 0.83 for the charcoal cookie and 1.08 ± 0.70 for the charcoal suspension ($p=0.001$). For one subject the charcoal cookie VAS was inadvertently not recorded during the study visit.

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

Discussion

This is the first clinical trial showing that a charcoal cookie effectively adsorbs a drug substance (cimetidine), similar to aqueous charcoal slurry. The cookie reduced cimetidine AUC and Cmax by approximately 82% and 64%, respectively. We found no difference in the relative effectiveness of the

charcoal cookie and aqueous charcoal slurry, which is the only comparative product available. It is known to adsorb various drugs and other compounds, preventing or minimizing absorption into the systemic circulation. Human volunteer studies demonstrate that activated charcoal is most beneficial if administered within one hour of drug ingestion. In 40 volunteer studies, administration of 50 g or more of activated charcoal within 30 minutes of drug administration resulted in a mean reduction of bioavailability of 47%.² 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 is administered at 15 minutes after the cimetidine dose is consistent with these previous studies.

We describe unusual pharmacokinetic findings in one subject. This subject appeared to absorb more cimetidine with the charcoal slurry than with cimetidine alone. This same subject experienced a decrease in cimetidine 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 administration of charcoal 15 minutes after cimetidine did not reduce drug absorption. Data analysis performed with and without this outlier showed similar findings.

Early administration of activated charcoal maximizes reduction in toxin absorption. For adult overdose patients requiring treatment in a health care facility, the time interval between ingestion and arrival in the Emergency Department is usually over one hour.¹¹ Treatment is further delayed by time for triage and assessment by medical staff in the Emergency Department. A study of pre-hospital use of activated charcoal found that patients received activated charcoal in the ambulance an average of 46 minutes earlier than patients who received it in the Emergency Department.¹² Availability of a product that can

be easily administered in the pre-hospital 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 product and 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 raise 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 home¹³ or a simulated home environment.¹⁴ 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.¹⁵ There is a need for a pleasant tasting 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.^{10,16,17} The VAS 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 to smiling faces). Uses for VAS scales include assessment of pain and of appetite sensations (i.e, visual appeal, smell, taste, palatability). Examples of VAS 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.^{10,16} However, adding flavoring agents to the activated charcoal slurry is discouraged since these substances may decrease the adsorptive capacity of the charcoal. This study evaluated the efficacy (i.e. adsorptive capacity) of a charcoal cookie

formulation to reduce cimetidine absorption and compared its palatability to that of a commonly used aqueous charcoal preparation. 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.

This 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. While this timeframe is not feasible for the majority of overdoses in adults that are treated in the Emergency Department, it may be a reasonable time interval for use of charcoal in the home or by pre-hospital providers. Finally, preference for the cookie over the charcoal slurry in adults may not be generalizable to children.

Conclusions

A novel charcoal cookie formulation appears to be as effective as aqueous charcoal suspension at reducing absorption of cimetidine. The charcoal cookie is 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.

Acknowledgements

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

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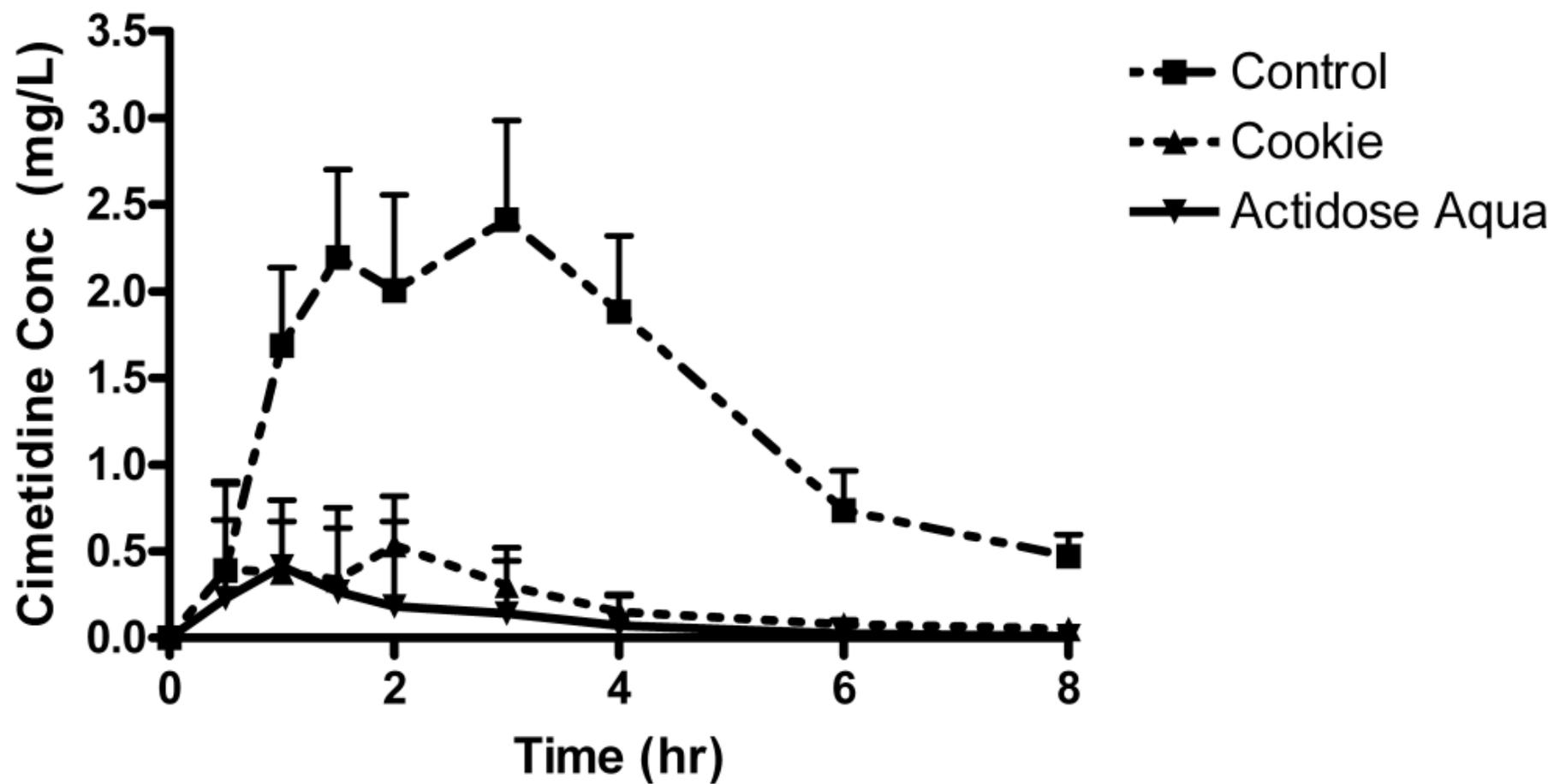
Table 1. Baseline demographics of study subjects

Subject #	Age (years)	Gender	Race/Ethnicity	Weight (kg)
1	22	Female	Hispanic	50.5
2	19	Male	Caucasian	61.4
3	20	Male	African American	66.4
4	23	Male	Hispanic	71.2
5	21	Female	Caucasian	117.7
6	20	Female	Caucasian	87.3
7	27	Male	Caucasian	82.7
8	35	Male	African American	102.3

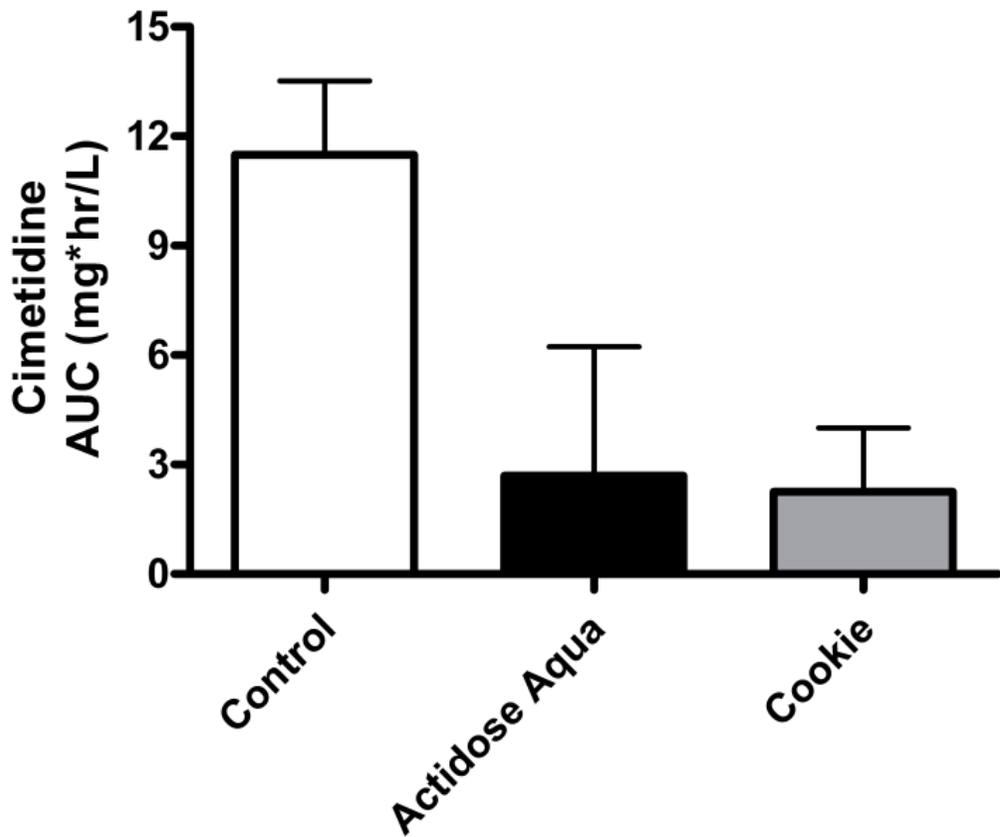
Table 2. Pharmacokinetics of cimetidine following oral administration of charcoal preparations

Subject	AUC (mg*hr/L)					Cmax (mg/L)				
	Actidose	Charcoal		Cimetidine		Actidose	Charcoal		Cimetidine	
Number	Aqua	%diff	Cookie	%diff	(Control)	Aqua	%diff	Cookie	%diff	(Control)
1	0.74	-95.4	4.32	-73.3	16.21	0.30	-92.2	2.08	-45.8	3.84
2	1.30	-90.5	1.20	-91.2	13.68	0.62	-81.0	0.55	-83.2	3.27
3	8.62	-35.4	2.47	-81.5	13.36	2.39	-9.4	0.78	-70.5	2.64
4	8.17	12.6	5.31	-26.9	7.26	3.43	64.7	2.20	5.9	2.08
5	0.81	-93.2	0.33	-97.2	11.90	0.39	-89.4	0.11	-97.1	3.68
6	0.40	-94.0	0.59	-91.2	6.73	0.29	-84.1	0.46	-74.6	1.83
7	1.22	-88.9	1.91	-82.7	11.08	1.08	-53.2	0.98	-57.6	2.30
8	0.24	-95.9	1.87	-67.8	5.82	0.14	-89.7	0.84	-37.5	1.34
Median	1.02*	-91.8	1.89*	-82.1	11.49	0.51**	-82.6	0.81*	-64.0	2.47
IQR	0.57	-94.7	0.90	-91.2	7.0	0.30	-89.6	0.50	-78.9	2.00
	4.74	-62.2	3.40	-70.6	13.52	1.74	-31.3	1.53	-41.6	3.48

AUC=Area under the plasma concentration-versus-time curve; IQR=Interquartile range ; *p<0.01 vs. Cimetidine; **p<0.05 vs. Cimetidine



A



B

