Cimetidine absorption in humans during sucralfate coadministration

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Cimetidine absorption after a single 300 mg oral dose was evaluated in six normal subjects in the absence or presence of sucralfate. Sucralfate was ingested four times a day for 2 days prior to and for two additional doses on the day of cimetidine ingestion. Sucralfate coadministration had no statistically significant influence on the rate or extent of cimetidine absorption.

Keywords cimetidine sucralfate absorption interaction

Introduction

Sucralfate, a new entity among anti-ulcer agents, is the aluminum salt of sucrose octasulfate (Nagashima, 1981). The drug is not significantly absorbed after oral dosing and is believed to exert its anti-ulcer activity through a local action in the gastrointestinal tract (Bighley & Giesing, 1981). The compound forms highly polar polyanions when in solution and electrostatic and physical interaction with the damaged mucosa is believed to be important to the action of sucralfate (Nagashima & Hirano, 1980). Other effects on the gastrointestinal tract include the binding of pepsin (Yoshida *et al.*, 1980) and bile acids (Bruugsgard *et al.*, 1981), a delay in gastric emptying and an increase in gastric pH in animals (Borella *et al.*, 1979; Nagashima, 1981).

Since sucralfate is poorly absorbed, most of the dose remains in the gastrointestinal tract and therefore the potential exists for sucralfate to affect the bioavailability of coadministered drugs. Potential mechanisms of these interactions include adsorption, complexation, decreased dissolution due to altered pH, and the formation of a physical barrier to absorption.

Cimetidine is a H₂-receptor antagonist believed to exert its effect by blocking histamine-mediated increase of gastric acid secretion (Freston, 1982). Cimetidine serum concentrations have been shown to correlate with a decrease in gastric acid

secretion (Henn *et al.*, 1975; Gugler *et al.*, 1981b; Pancorbo *et al.*, 1982; Pounder *et al.*, 1976).

Although increased efficacy of combining cimetidine and sucralfate for ulcer therapy remains unproven it is likely that for some patients clinicians will attempt to combine treatments in hope of an additive or synergistic effect. In a recent study (Van Deventer *et al.*, 1984), the 2 week healing rate from combined therapy in 61 subjects with duodenal ulcer approached a statistically significant difference compared to therapy with sucralfate or cimetidine alone. The influence of cimetidine on the binding of sucralfate to the ulcer crater has been examined in animals; with the doses used, cimetidine did not reduce the binding of sucralfate to ulcerated mucosa (Lacz *et al.*, 1983; Steiner *et al.*, 1982).

Several studies have examined the influence of sucralfate coadministration on the absorption of selected drugs in dogs and in most instances absorption was unaltered (Lacz *et al.*, 1982a,b). However, sucralfate has been shown to reduce phenytoin absorption by 38% (Lacz *et al.*, 1982b). Digoxin absorption in man is essentially unaffected (Giesing *et al.*, 1983), while sucralfate may interfere with warfarin absorption (Mungall *et al.*, 1983). Cimetidine absorption in dogs was reduced by 18% with concomitant sucralfate administration (Lacz *et al.*, 1982a). In contrast, a

more recent report (Ritschel *et al.*, 1984) indicated that sucralfate reduced the rate but not the extent of cimetidine absorption in dogs. The *in vitro* binding of cimetidine to sucralfate in human gastric fluid at different pHs was shown to be unaffected by different concentrations of sucralfate (Boivin *et al.*, 1983).

The purpose of this study was to determine if sucralfate coadministration altered either the rate or extent of cimetidine absorption in humans.

Methods

The study was conducted as a randomized cross-over trial of cimetidine with or without sucralfate coadministration. Six healthy male volunteers (27–42 years) on no concurrent medications served as subjects after providing written informed consent. The subjects initially received cimetidine and sucralfate or cimetidine alone. The dose of cimetidine was a single 300 mg tablet that was administered on the morning of the trial with 8 oz of water. All tablets were from the same manufacturer's lot (Tagamet®). Subjects fasted overnight and for 3 h after the dose of cimetidine. Standard meals were served at 3 and 7 h after the dose. A 1 g sucralfate tablet (Carafate®) was ingested four times a day (1 h before meals and at bed time) for 2 days prior to the dose of cimetidine, with the dose of cimetidine, and with the standard lunch during the sucralfate phase of the trial. There was a 7 day washout period before subjects crossed over to the alternate phase.

An indwelling venous catheter was placed into a forearm vein prior to the dose of cimetidine. Catheters were flushed with 1 ml of dilute heparin solution after each blood sample to maintain catheter patency. Before obtaining blood samples, 2 ml of blood were drawn into a separate syringe and discarded to prevent sample dilution. Blood samples were drawn into Vacutainer tubes without anticoagulants and blood was allowed to clot before centrifugation. Serum samples were separated from whole blood and stored frozen until the time of analysis. All samples were collected at the following times relative to the cimetidine dose: 0, 0.25, 0.5, 0.75, 1.0, 1.25, 1.5, 1.75, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 6.0, 8.0, and 10 h.

Serum samples were analysed for cimetidine using a modification of the high pressure liquid chromatographic method of Mihaly *et al.* (1982). Serum (1 ml) containing the internal standard (metiamide, 1.5 µg) was alkalized (50 µl 2 N NaOH) and extracted with 5 ml methylene chloride. The organic phase was separated, placed into a fresh tube and evaporated under a

stream of nitrogen at 30° C. The mobile phase was used for reconstitution (50 or 100 µl) and 20 µl was injected onto the column. The mobile phase consisted of 12% acetonitrile, 0.025% triethylamine and monopotassium phosphate (5 mmol), adjusted to a final pH of 3.44 with phosphoric acid. The mobile phase (1.1 ml min⁻¹) was passed through a reverse phase C-18 column (Ultrasphere ODS, 5 µ, 25 cm × 4.6 mm internal diameter, Altex Scientific Inc., Berkeley, CA.). Cimetidine was detected at 229 nm using a fixed wavelength UV detector. Quantification was achieved with reference to a standard curve (prepared in each subject's serum) of peak height ratio vs cimetidine concentration. The standard curves were linear over the range of 100 to 3000 ng ml⁻¹. The within-day percentage coefficients of variation (5 replications) at 300, 1250 and 1750 ng ml⁻¹ were 7.2, 5.8 and 3.5%, respectively. The between-day percentage coefficients of variation (eight replications) at 300 and 1750 ng ml⁻¹ were 11.2 and 7.8%, respectively. The retention times for cimetidine and internal standard were 5.95 and 6.50 min, respectively. The investigator performing the analysis was unaware of the source of the samples.

The cimetidine serum concentration–time data were analysed by model-independent area methods. The terminal elimination rate constant (*k*) was computed using a log-linear regression of points determined to be in the terminal elimination phase. The half-life (*t*_{1/2}) was determined by $t_{1/2} = 0.693 k^{-1}$. The areas under the concentration–time curves (AUC) were calculated using the linear trapezoidal rule. The area from the last measured time to infinity was calculated by dividing the point on the regression line at that time (*C_t*) by the elimination rate constant. The area under the first moment curve (AUMC) was also calculated using the linear trapezoidal rule. The area from the last measured time to infinity was calculated using the formula, $C_t/k^2 + C_t^*/t/k$. The mean residence time (MRT) was calculated by dividing the AUMC by AUC. The mean absorption time (MAT) was determined by, $MAT = (MRT)_{oral} - (MRT)_{i.v.}$, where (MRT)_{oral} is the mean residence time of cimetidine administered by the oral route in the absence or presence of sucralfate and (MRT)_{i.v.} is the mean residence time of cimetidine after an intravenous bolus. Although MAT cannot be exactly determined since an intravenous dose was not administered, MAT will be proportional to (MRT)_{oral}, assuming that (MRT)_{i.v.} is the same in the presence or absence of sucralfate (*i.e.*, no change in cimetidine disposition). Further assuming a one-compartment model, MAT is inversely related to the absorption rate constant.

Therefore, the ratio of (MRT) oral determined in the absence of sucralfate to that in the presence of sucralfate will be proportional to the ratio of the absorption rate constants in the presence of sucralfate to that in the absence of sucralfate.

The calculated parameters for cimetidine with and without sucralfate were compared using the Student's *t*-test for matched pair analysis. A *P* value of < 0.05 was considered significant.

Results

All subjects completed the study according to the protocol except for subject 6. This subject did not begin sucralfate dosing until the evening before cimetidine administration during the sucralfate phase of the study.

The concentration-time curves for all subjects are shown in Figure 1. The data for all subjects demonstrated discontinuous absorption of cimetidine in both phases of the study. The calculated parameters for each of the six subjects and the mean values are listed in Table 1. Sucralfate did not significantly affect the extent of absorption as determined by the ratio of AUCs.

Sucralfate, as expected, did not significantly affect the elimination characteristics of cimetidine based upon the values for the elimination rate constants. Our assumption that differences in MRT between the trials reflect differences in absorption seems valid. The non-statistically significant differences in MRT reflect a non-statistically significant difference in MAT. The model-independent method utilized does not allow for the exact calculation of an absorption rate constant for cimetidine but only the ratio of those constants with and without sucralfate.

Discussion

A number of investigators have shown a significant positive correlation between plasma concentrations of cimetidine and the inhibition of gastric acid secretion (Henn *et al.*, 1975; Gugler *et al.*, 1981b; Pancorbo *et al.*, 1982; Pounder *et al.*, 1976). Thus, it is important to recognize that drugs which decrease the absorption of cimetidine may decrease its efficacy. Cimetidine absorption has been shown to be significantly decreased by concurrent administration of antacids with rela-

Figure 1 Individual cimetidine serum concentration-time profiles in the absence (●) and in the presence (○) of sucralfate in six healthy volunteers. The straight lines represent linear regression fits of the terminal data.

Table 1 Cimetidine absorption and elimination parameters in the absence (C) and presence of sucralfate (C+S)

Subject	$t_{1/2}$ (h) ¹		AUC ($\mu\text{g ml}^{-1} \text{h}$) ²			MRT (h) ³		
	C	C+S	C	C+S	C+S/C	C	C+S	C/C+S
1	1.5	1.9	3.36	4.08	1.21	4.0	3.5	1.14
2	2.5	1.9	6.43	6.77	1.05	3.4	4.2	0.81
3	2.0	2.0	8.75	9.13	1.04	3.4	3.2	1.06
4	1.6	2.1	7.01	5.67	0.81	3.9	3.9	1.00
5	1.9	1.8	7.11	9.51	1.34	4.1	3.8	1.08
6	1.9	2.4	6.27	7.29	1.16	4.0	3.5	1.14
Mean	1.8 ⁴	2.0 ⁴			1.10	3.8	3.7	1.04
$\pm$ s.d.	0.3 ⁵	0.2 ⁵			$\pm$ 0.18	0.3	0.4	0.12
Statistical comparison ⁶	NS ⁷		NS			NS		

1 Elimination half-life

2 Area under the cimetidine serum concentration-time curve from time 0 to infinity.

3 Mean residence time.

4 Harmonic mean.

5 'Pseudo' standard deviation (Lam *et al.*, 1985).6 NS = not significantly different ($P > 0.05$).

7 Statistical test performed on the elimination rate constant values.

tively high (85–150 mmol HCl) but not low (20–50 mmol HCl) neutralizing capacity (Bodemar *et al.*, 1979; Burland *et al.*, 1976; Gugler *et al.*, 1981a; Steinberg *et al.*, 1982). Although sucralfate does alter gastric pH (buffer capacity of 1 g sucralfate $\approx$ 13 mmol H⁺) its main mechanism of action is not likely to be as an antacid (Bighley & Giesing, 1981).

The influence of sucralfate on the absorption of a variety of drugs has been examined in dogs. Coadministration has been shown not to influence the absorption of aspirin (Lau *et al.*, 1985), digoxin, quinidine, propranolol, aminophylline, diazepam, imipramine, chlorpromazine and ethynyl estradiol (Lacz *et al.*, 1982a,b). Tetracycline absorption is unimpaired when the drugs are given 2 h apart (Lacz *et al.*, 1982b); whereas, phenytoin absorption decreases by 38% upon concomitant ingestion (Lacz *et al.*, 1982b). The latter effect may be avoided by giving the drugs at different times. In humans, digoxin absorption rate appears to increase while the extent of absorption is unaltered (Giesing *et al.*, 1983). Sucralfate may also be responsible for altered warfarin absorption in man (Mungull *et al.*, 1983), although a recent study indicates the absence of an interaction (Talbert *et al.*, 1985).

There have been two studies conducted in dogs which have examined the influence of sucralfate on cimetidine absorption. One study reports an 18% decrease in cimetidine absorption (Lacz *et al.*, 1982a), while in the other study there was a decrease in rate but no change in the extent of absorption (Ritschel *et al.*, 1984). The results of the present study in humans indicate that sucralfate

coadministration has no significant effect on either the rate or completeness of cimetidine absorption (Table 1). In both animal studies an oral solution of radiolabeled cimetidine was used. In the study of Lacz *et al.* (1982a), 1 g sucralfate tablets were administered three times a day for 2 days prior to and with the cimetidine dose. Our protocol employed a similar dosing schedule. The study of Ritschel *et al.* (1984) appears to have involved only a single 1 g dose of sucralfate tablets 1 h prior to cimetidine administration. While there were some differences in the experimental methods employed in these studies, there are no obvious explanations for the different findings. Lacz *et al.* (1982a), also indicate that the interaction between sucralfate and cimetidine can be avoided by spacing the time between ingestion of each drug. This appears to be true whenever other interactions with sucralfate have been observed (e.g., phenytoin, tetracycline) (Lacz *et al.*, 1982b).

The discontinuous absorption of cimetidine is an interesting property of this compound that has been noted in a number of other studies (Bodemar *et al.*, 1977; Grahnen *et al.*, 1979; Walkenstein *et al.*, 1978). Several mechanisms have been proposed to explain this observation including uptake into hepatic parenchymal tissue and bile with subsequent release of drug into the intestine (Pederson & Miller, 1980) and variable absorption from different anatomic regions of the intestine (Griffith *et al.*, 1977).

Although the exact mechanism to explain discontinuous absorption remains to be elucidated, we believe that some form of enterohepatic

cycling or direct gastrointestinal secretion of the drug into the intestine represents the most plausible explanation.

A potential limitation of this study is that it was conducted in persons with normal intestinal and stomach mucosa. As the binding of sucralfate occurs preferentially to ulcerated mucosa, the

binding may be different in subjects with normal mucosa (Nagashima & Hirano, 1980). We believe that any such differences are likely to be minimal and as there was no trend towards decreased cimetidine bioavailability with sucralfate, a clinically significant interaction in patients is unlikely.

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