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The comparative bioavailability of cimetidine-alginate treatments

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Abstract—The comparative bioavailability of cimetidine in cimetidine-alginate combinations has been investigated in twelve healthy volunteers in an open crossover study. Each volunteer received a single oral dose of a commercially available alginate-cimetidine combination tablet (Algitec) or cimetidine tablets (Tagamet), co-administered with a commercially available alginate reflux suppressant liquid or tablet (Gaviscon). No significant differences were observed between treatments for C_{max}, t_{max}, AUC_{0-12} or $AUC_{0-\infty}$. The study demonstrated equivalent bioavailability of cimetidine when administered separately with alginate products and as a fixed dose combination product.

Cimetidine is a potent and selective histamine H_2-receptor antagonist used in the treatment of various gastrointestinal disorders (Dyck 1979). It inhibits basal and stimulated gastric hydrochloric acid secretion, and reduces the output of pepsin (Bavin et al 1984). Alginate/antacid combinations have been shown to be effective in reducing the frequency and duration of symptoms of acid reflux in patients (Stanciu & Bennett 1974; Williams et al 1979; Braniki et al 1988). Alginate formulations produce viscous gels of near neutral pH which float on the stomach contents. The gel forms a physical barrier, preventing the reflux of gastric contents into the oesophagus. Alginate products and cimetidine are frequently co-prescribed because of their complementary modes of action. However, a recent report concluded that alginate could decrease and slow the absorption of cimetidine when presented as a specifically formulated combination product (Boyko & Lamb 1988). This study was undertaken to compare the bioavailability of cimetidine in healthy non-patient volunteers following administration of single oral doses of the alginate-cimetidine combination tablet (Algitec) and cimetidine tablets (Tagamet) co-administered with a commercially available alginate reflux suppressant liquid or tablet (Gaviscon).

Materials and methods

The study was of a randomized three-treatment crossover design with at least five days interval between treatments. Twelve healthy adult volunteers (four non-pregnant female and eight male, age 18–38 years, weight within 15% of ideal body weight) who had passed a full medical examination, including ECG, as well as having normal blood biochemical and haematological parameters measured within two weeks before the study, were recruited. None of the subjects had taken inappropriate medication in the two weeks before the trial, or were allergic to cimetidine. Written informed consent was obtained from all participants. The study was carried out according to the guidelines for the Declaration of Helsinki (Tokyo amendment).

The fasted volunteers reported at 0730 h on the morning of each study period, when they were given a standard light breakfast. Before dosing, a blood sample (10 mL) was collected from an i.v. catheter inserted into a suitable peripheral vein, around the antecubital fossa, for baseline reference of plasma cimetidine concentration. No food or drink was permitted until four hours after the dose, when a standard lunch was provided. An evening meal was provided ten hours after dosing. Intake of fruit juice was unrestricted.

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The volunteers received either treatment A, B or C with the order of dosing randomized using a Williams squares design.

Treatment A. One combination tablet containing cimetidine (200 mg) and alginic acid (500 mg), thoroughly chewed, and followed by 150 mL of tap water.

Treatment B. One cimetidine tablet (200 mg), swallowed with 50 mL of tap water and 10 mL of sodium alginate liquid (500 mg), followed by 90 mL of tap water.

Treatment C. One cimetidine tablet (200 mg), swallowed with 50 mL of tap water, then one alginic acid tablet (500 mg), thoroughly chewed, followed by 100 mL of tap water.

Blood samples (10 mL) were obtained before and at 0·25, 0·5, 0·75, 1·0, 1·5, 2·0, 2·5, 3·0, 4·0, 6·0, 8·0, 10·0 and 12·0 h after drug administration. The samples were immediately transferred to heparinized tubes and gently mixed. After centrifugation (3000 rev min^{-1} for 10 min) the supernatant plasma was separated and stored deep-frozen (−10°C) until required for analysis. The concentration of cimetidine in plasma was determined by HPLC (concentration range 0·05–5·0 $\mu g\ mL^{-1}$). The coefficient of variation of the assay procedure was 16·0%.

Each group of test samples included two quality control samples (blank plasma with added cimetidine and internal standard) to check assay performance. Additionally, 15% of the samples were subjected to repeat analysis to evaluate assay performance over the study period. The residual standard deviation based on $\log_e$ transformed duplicates was found to be 0·135 (i.e. approximately 11% in terms of untransformed data), which is considered acceptable for a procedure of this type.

Pharmacokinetics. Model independent pharmacokinetic parameters were calculated on a Hewlett-Packard Vectra computer using Simed Siphar software (Simed, France), as follows:

(i) *Half-life.* The elimination rate (K_{el}) was calculated by regression analysis of the linear terminal phase of the plasma concentration - time curve and used to calculate half-life ($t_{\frac{1}{2}}$) from the following relationship:

$$t_{\frac{1}{2}} = \log_e 2 / K_{el} \quad (1)$$

(ii) *Area under the plasma concentration - time curve.* Area under the curve (AUC) was calculated from the actual data points as AUC_{0-12} using the linear trapezoidal rule (Gibaldi & Perrier 1982), and extrapolated to infinity using the following equation:

$$AUC_{0-\infty} = AUC_{0-12} + \frac{c_{12}}{K_{el}} \quad (2)$$

Where c_{12} = plasma concentration at 12 h.

(iii) *C_{max} and t_{max}.* Maximum concentration (C_{max}) and time to reach this maximum (t_{max}) were determined by visual inspection of the individual plasma concentration - time curves.

Results and discussion

Table 1 shows mean plasma concentrations (±s.e.m.) for treatments A, B, and C. Because of the withdrawal from the

Table 1. Mean plasma concentrations (±s.e.m.) of cimetidine for treatments A, B and C.

Time after administration (h)	Mean plasma concn ± s.e.m. ($\mu g\ mL^{-1}$)		
	A (n = 12)	B (n = 11)	C (n = 12)
0	ND	ND	ND
0·25	ND	ND	ND
0·5	0·14 ± 0·03	0·07 ± 0·05	0·06 ± 0·03
0·75	0·27 ± 0·04	0·26 ± 0·11	0·18 ± 0·09
1·0	0·50 ± 0·10	0·48 ± 0·13	0·30 ± 0·09
1·5	0·58 ± 0·06	0·67 ± 0·09	0·55 ± 0·10
2·0	0·67 ± 0·04	0·71 ± 0·06	0·73 ± 0·07
2·5	0·61 ± 0·03	0·66 ± 0·04	0·66 ± 0·05
3·0	0·52 ± 0·05	0·57 ± 0·07	0·53 ± 0·03
4·0	0·35 ± 0·03	0·38 ± 0·04	0·42 ± 0·05
6·0	0·21 ± 0·02	0·21 ± 0·02	0·22 ± 0·01
8·0	0·12 ± 0·01	0·10 ± 0·01	0·11 ± 0·01
10·0	0·07 ± 0·01	0·05 ± 0·01	0·06 ± 0·01
12·0	0·02 ± 0·01	0·03 ± 0·01	0·03 ± 0·01

ND = None detected, assumed to be 0·00 for statistical purposes.

study of volunteer 7 after the first two phases, results for treatment B are calculated using only 11 volunteers.

The pharmacokinetic parameters are shown in Table 2. Fig. 1 shows a plot of mean plasma concentration versus time. In all cases mean standard errors were less than 0·13 $\mu g\ mL^{-1}$.

Using analysis of variance for a Williams Squares design on both the untransformed and log transformed data, no significant differences were detected between treatments for C_{max}, t_{max}, AUC_{0-12} or $AUC_{0-\infty}$. The results were also analysed non-parametrically for t_{max} and $t_{\frac{1}{2}}$, giving the same conclusions. The power to detect a 20% difference at the 5% significance level in log transformed units for the above parameters was shown to be in excess of 90% for all except t_{max}.

Westlake 95% confidence intervals for the pharmacokinetic parameters were also estimated (Westlake 1976). These gave symmetrical limits expressed as percentages for treatments B and C relative to the combination tablet (treatment A) as the standard (Table 3). Based on a ±20% limit for AUC, equivalent bioavailability was established amongst all three treatments: t_{max} confidence intervals were relatively large for both treatments B and C (34·1% and 58·8%, respectively); however, these may be artificially high since t_{max} values correspond to preselected sampling times.

The Westlake confidence interval for C_{max} was ±18·2% for the cimetidine tablet and liquid alginate (treatment B) whereas a slightly higher value was obtained for the cimetidine tablet and alginate tablet (treatment C, 24·7%).

In conclusion, this study has demonstrated that co-administration of alginate with cimetidine in three different dosage forms has no effect on the relative bioavailability of cimetidine.

Table 2. Mean pharmacokinetic parameters.

Treatment	Mean parameter (±s.e.m.)				
	C_{max} ($\mu g\ mL^{-1}$)	t_{max} (h)	K_{el} (h^{-1})	AUC_{0-12} ($\mu g\ mL^{-1}\ h$)	$AUC_{0-\infty}$ ($\mu g\ mL^{-1}\ h$)
A	0·82 (0·06)	2·0 (0·2)	0·30 (0·02)	2·94 (0·15)	3·13 (0·17)
B	0·86 (0·06)	1·9 (0·3)	0·35 (0·02)	3·08 (0·17)	3·24 (0·18)
C	0·79 (0·07)	2·1 (0·1)	0·32 (0·02)	2·98 (0·21)	3·15 (0·21)

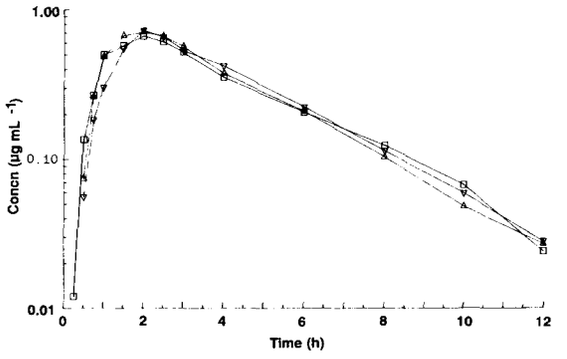

FIG. 1. Plasma concentrations versus time for treatments A, B and C (mean values). (□) A combination tablet, (△) B cimetidine tablet + liquid alginate, (▽) C cimetidine tablet + alginate tablet.

Table 3. 95% Westlake confidence interval relative to cimetidine-alginate tablet (treatment A).

Parameter	Treatment (%)	
	B	C
C_{max} ($\mu g\ mL^{-1}$)	±18·2	±24·7
t_{max} (h)	±34·1	±58·8
AUC_{0-12} ($\mu g\ mL^{-1}\ h$)	±8·8	±8·1
$AUC_{0-\infty}$ ($\mu g\ mL^{-1}\ h$)	±6·9	±7·1

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