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The effect of an antacid and food on the absorption of cimetidine and ranitidine

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Abstract—The effect of varying doses of a liquid antacid preparation containing magnesium hydroxide, aluminium hydroxide and simethicone on the absorption of the H_2-receptor antagonists, cimetidine and ranitidine, was determined in 2 groups of 11 volunteers; one group fasted and one group fed a standardized breakfast. The antacid alone caused a significant decrease in the AUC of cimetidine (24%). Similarly, concomitant antacid caused a 59% decrease in the AUC of ranitidine. There were no effects on any of the other pharmacokinetic parameters examined. The absorption of both drugs was similar in fasted and fed volunteers, but in the fed volunteers the antacid did not produce the decrease in AUC seen in the fasted volunteers. These data suggest that H_2-receptor antagonists should not be taken at the same time as antacids.

Antacids are frequently recommended for the relief of pain during the first few days of treatment with an H_2-receptor antagonist. But their effects on the absorption and effectiveness of these antagonists should appear inconsistent. For example, Mihaly et al (1982) found a 33% reduction in peak plasma concentration and AUC of ranitidine after administration of an antacid, whilst Frislid & Berstad (1983) and Eshelman et al (1983) were unable to detect an effect of either antacid or food on ranitidine kinetics. Early studies with cimetidine (Burland et al 1976; Bodemar et al 1978, Walkenstein et al 1978) indicated no effect of antacids on its bioavailability, whilst Bodemar et al (1979) and Steinberg & Lewis (1980) have shown that co-administration of 30 mL of Mylanta II caused a 33% drop in peak concentration and a 33% drop in mean AUC. Those studies however, examined various combinations of antacid doses and cimetidine or ranitidine and used varying sampling regimes to estimate pharmacokinetic parameters.

In view of the frequent use of these two H_2-receptor antagonists with antacids, and of the propensity of patients to take drugs with meals, even if instructed not to do so, we have examined the effects of antacids on blood concentrations attained after oral administration of the two H_2-receptor antagonists in both fed and fasted subjects.

Materials and methods

Subjects. Eighteen healthy male volunteers (18 to 29 years), who were on no other medications participated. The experiment, as set out below, was conducted in two groups of 11, with four of the volunteers involved in both. One group consumed a standard breakfast (09.00 h) before beginning the study (see below) whereas the other group fasted until lunchtime (13.00 h).

Procedure. Each subject was studied on six occasions separated by at least one week. On each occasion, after an overnight fast, an indwelling venous catheter was inserted in a forearm and a predose 10 mL baseline sample of blood was taken. Each subject then received one of the following treatments; (a) cimetidine 400 mg only, (b) ranitidine 150 mg only, (c) cimetidine 400 mg and antacid 10 mL at 0, 1 and 3 h, (d) ranitidine 150 mg and antacid 10 mL at 0, 1 and 3 h, (e) cimetidine 400 mg and antacid 45 mL at 0, 1 and 3 h and (f) ranitidine 150 mg and antacid 45 mL at 0, 1 and 3 h.

Treatments (a) and (b) were taken with 100 mL of water. Treatments involving antacid were taken with water to a total volume of 100 mL. The doses of antacid and water were repeated, as indicated above, at 1 and 3 h post-dose. The order in which an individual received these six treatments was randomized.

Blood samples were taken on each occasion through the indwelling venous catheter into lithium heparin tubes at 10, 20, 30, 45, 60, 75, 90, 105, 120, 150, 180, 210, 240, 270, 300, 360 and 480 min post-dose. The samples were immediately centrifuged and the plasma separated and stored at −20 °C until assay.

Four h after dosing, volunteers were served a standardized cold lunch.

Blood and urine samples were taken from each volunteer, on the first and last day of study in each of the two treatment phases, for routine haematological and biochemical analysis. All results from these samples were within normal limits.

The experiment was repeated using the group taking a standardized breakfast 15 min before the dose of cimetidine or ranitidine. The breakfast consisted of cereal and milk, toast, egg and coffee.

Drugs. Cimetidine was taken as a single 400 mg tablet (Tagamet, Smith, Kline & French Laboratories); ranitidine as a single 150 mg tablet (Zantac, Glaxo). Liquid antacid (Mylanta, Parke-Davis) taken from freshly opened bottles, contained magnesium hydroxide 400 mg, aluminium hydroxide 400 mg and simethicone 40 mg per 10 mL, with a neutralizing capacity of 22 mmol per 10 mL.

Assay Methods. Cimetidine and ranitidine were assayed by HPLC using slight modifications of published methods (Mihaly et al (1980a, b). Minimum detectable concentrations from 1 mL of sample were 15 and 30 ng mL^{-1} for cimetidine and ranitidine, respectively.

Data handling. Plasma concentration time curves were constructed for each study. Area under the curve (AUC) was determined by trapezoidal rule with extrapolation to infinity of the calculated terminal slope. Terminal half-life ($t_{\frac{1}{2}}$) and slope of the absorption upstroke (K_{up}) were calculated manually by least squares regression. Other data recorded included time to peak (T_{max}) and peak concentration (C_{max}) of the drug under investigation. For each drug, the effect of antacid preparation and food on each of these pharmacokinetic parameters were assessed using an analysis of variance (ANOVA) using program GENSTAT. Individual differences were tested using Tukey's method.

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Table 1. Effect of increasing doses of antacid on the pharmacokinetics of cimetidine and ranitidine in fasting subjects (mean ± s.e.m.).

Antacid (mL) dose	AUC ($\mu g\ mL^{-1}\ h$)	$t_{\frac{1}{2}}$ (h)	K_{up} (h^{-1})	C_{max} ($\mu g\ mL^{-1}$)	T_{max} (h)
Cimetidine					
0**	6·37 ± (0·67)	2·15 ± (0·26)	3·86* ± (1·06)	1·59 ± (0·34)	0·94 ± (0·11)
10	5·17 ± (0·53)	2·27 ± (0·26)	2·87 ± (0·91)	1·21 ± (0·21)	1·08 ± (0·14)
45	4·86 ± (0·31)	2·56 ± (0·60)	2·79 ± (0·76)	1·16 ± (0·25)	1·08 ± (0·13)
Ranitidine					
0	2·15 ± (0·45)	2·36 ± (1·07)	1·86 ± (0·58)	0·34 ± (0·06)	1·25 ± (0·21)
10	1·58 ± (0·26)	2·77 ± (0·35)	2·22 ± (0·65)	0·28 ± (0·06)	1·32 ± (0·15)
45	0·88 ± (0·13)	2·34 ± (0·46)	1·51 ± (0·31)	0·22 ± (0·02)	0·96 ± (0·11)

* K_{up} could not be calculated in one subject due to insufficient data points before the peak, thus n = 9.
** One curve did not conform to exponential decline, thus n = 10.

Table 2. Effect of increasing doses of antacid on the pharmacokinetics of cimetidine and ranitidine in fed subjects (mean ± s.e.m.).

Antacid (mL) dose	AUC ($\mu g\ mL^{-1}\ h$)	$t_{\frac{1}{2}}$ (h)	k_{up} (h^{-1})	C_{max} ($\mu g\ mL^{-1}$)	T_{max} (h)
Cimetidine					
0	5·92 ± (0·56)	1·93 ± (0·22)	2·99 ± (0·56)	1·97 ± (0·26)	1·13 ± (0·15)
10	4·73 ± (0·35)	2·14 ± (0·23)	3·74 ± (0·69)	1·60 ± (0·17)	1·21 ± (0·13)
45	5·32 ± (0·63)	1·58 ± (0·13)	3·29 ± (0·80)	1·89 ± (0·26)	1·39 ± (0·21)
Ranitidine					
**0	1·70 ± (0·25)	2·26 ± (0·25)	2·84* ± (0·39)	0·39 ± (0·05)	1·23 ± (0·12)
10	1·99 ± (0·18)	2·19 ± (0·24)	2·41 ± (0·34)	0·50 ± (0·05)	1·26 ± (0·11)
45	2·09 ± (0·25)	2·05 ± (0·26)	2·76 ± (0·75)	0·43 ± (0·05)	1·41 ± (0·22)

* K_{up} could not be calculated in one subject due to insufficient data points before the peak, thus n = 7.
** One curve did not conform to exponential decline, thus n = 9.

Ethics. The study was approved by the Ethics Committee of St. Vincent's Hospital and all volunteers gave informed written consent.

Results

The results for the fasting subjects are given in Table 1 and the fed subjects in Table 2. There were no statistically significant differences in any of the pharmacokinetic parameters within either group or between groups except for AUC.

In the fasting subjects, the co-administration of the antacid with cimetidine was associated with a reduction in AUC. Compared with the control there was a 19% fall in the AUC when 10 mL of antacid was given and a decrease to 24% when 45 mL was given. Similarly, with ranitidine, in the fasted state, co-administration of 10 mL antacid was associated with 27% decrease in AUC, whilst a 45 mL dose caused a decrease of 59%. In the fasting subjects, there was a significant linear effect of antacid dose on the AUC of both H_2 receptor antagonists ($P < 0·05$). In the fed subjects, there was no effect of antacid on AUC of either cimetidine or ranitidine.

The joint 95% confidence intervals derived by Tukey's method between antacid levels for differences in AUC for cimetidine and ranitidine (analysed together) in the fasting group are given in Table 3. There was a significant difference between control and 45 mL dose.

Table 3. Joint 95% confidence intervals for differences in AUC of cimetidine and ranitidine (analysed together) between antacid levels, in the fasting group.

Pairwise comparison	Estimate	Joint 95% confidence intervals
0–10	0·86	−0·08, 4·44
0–45	1·37	0·43, 2·31
10–45	0·51	−0·43, 1·45

The cimetidine and ranitidine studies without antacid, showed no difference in AUC for either group.

Discussion

The results obtained confirm that co-administration of any antacid preparation with cimetidine to fasting subjects caused a significant decrease in AUC of cimetidine related to the dose of antacid as has previously been suggested by Burland et al (1976) and Walkenstein et al (1978). In subjects who had taken a meal 15 min before dosing, there was no effect on the AUC of cimetidine given alone but the presence of food virtually abolished the interaction between the antacid preparation and cimetidine seen when the subject was fasting.

The effect of co-administration of the antacid preparation on the AUC of ranitidine in fasted subjects was similar but greater than that with cimetidine. The decrease of 59% was comparable to that reported by Mihaly et al (1982). In a different group of subjects, consumption of breakfast abolished the effect of the antacid preparation on AUC of ranitidine.

The AUC of a drug may be affected by its absorption or its elimination. If the latter were the case, the $t_{\frac{1}{2}}$ would be expected therefore to diminish, but no consistent effect of antacid on $t_{\frac{1}{2}}$ was found. It is therefore likely that the differences in AUC reflect changes in absorption. Other values which may be expected to reflect changes in absorption, such as K_{up}, the slope of the upstroke of the concentration-time curve, or C_{max} or T_{max}, were not reproducibly affected by either antacid or food. However, a double peak in the plasma-concentration time curves for both cimetidine and ranitidine was seen in most subjects. This is consistent with the observations made by Mihaly et al (1980a) and it may have obscured changes in the curves.

A likely explanation of these results is that the presence of the antacid impairs dissolution of the tablets or that the dissolved drug is bound to the unabsorbed antacid. The abolition of antacid effects in the presence of food could be due to competition for drug binding sites on the antacid gel. The study indicates that antacids of the type used should not be taken in close proximity to H_2- receptor antagonists.

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Chronic administration of MK-801 and the NMDA receptor: further evidence for reduced sensitivity of the primary acceptor site from studies with the cortical wedge preparation

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Abstract—Cortical slices removed from rats pre-treated with MK-901 0.5 mg kg^{-1} twice a day for 7 days had reduced responses to *N*-methyl-D-aspartate (NMDA) relative to quisqualate and glutamate compared with control animals. Potencies of competitive (CPMP) and non-competitive (ketamine) NMDA antagonists appeared unchanged. These changes are consistent with a reduced density of NMDA receptors.

MK-801 ((+)-5-methyl-10, 11-dihydro-5H-dibenzo-[a, d] cyclo-hepten-5, 10-imine) has recently attracted considerable attention because it protects against neuronal degeneration following ischaemic and hypoglycaemic episodes. Additionally, MK-801 readily crosses the blood-brain barrier and is a potent anticonvulsant (see Manallack et al 1988, 1989). MK-801 has many actions in common with phencyclidine (PCP)-like molecules (Manallack et al 1988) and acts via the PCP site in the ionophore of the *N*-methyl-D-aspartate (NMDA) subtype of L-glutamate (Glu) receptor to produce a "use-dependent", non-competitive blockade (Davies et al 1988b). Recently, to gain insights into the regulation of the NMDA receptor, we studied the effects of the chronic administration of MK-801 on various indices reflecting the functioning of the domains of the NMDA receptor (Manallack et al 1989). Despite behavioural tolerance to the actions of MK-801, neither the number nor density of PCP site was altered, whilst there was a down-regulaton (50% decrease) of cortical sites for [^{3}H]-D-2-amino-5-phosphonopentanoic acid. These data suggested differential regulation of the domains of the NMDA receptor and adaptations of the primary acceptor site for agonists/antagonists in response to MK-801 treatment. To provide further insight into functional adaptations of the NMDA receptor-ionophore complex we have investigated the effects of chronically administered MK-801 using the "cortical wedge" preparation.

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Methods and results

Male Sprague-Dawley rats (200-250g) received intraperitoneal injections of MK-801 as previously described (2 × daily, 0·5 mg kg^{-1}, 7 days), except that the interval between the last injection