Ranitidine and cimetidine; drug interactions with single dose and steady-state nifedipine administration

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1 The effect of ranitidine 300 mg once daily and cimetidine 800 mg once daily on the disposition of nifedipine was studied in two groups of 12 volunteers. Both investigations were placebo-controlled cross-over studies.

2 The first group received ranitidine, cimetidine or placebo for 5 days with 20 mg nifedipine given on the 5th day. Each period was separated by 1 week. The second group received nifedipine 10 mg three times daily for 5 days together with the H₂-receptor antagonist or placebo.

3 Cimetidine produced a significant increase in the AUC of both single and steady state dosing of nifedipine. Peak nifedipine levels were significantly increased only in the chronic dose study compared to placebo.

4 Ranitidine did not produce any significant changes in either study.

Keywords ranitidine cimetidine nifedipine

Introduction

It is well established that cimetidine inhibits liver enzymes involved in drug metabolism (Henry *et al.*, 1980; Pelkonen & Puurunen, 1980; Puurunen *et al.*, 1980; Borm *et al.*, 1981; Rollinghoff & Paumgartner, 1982; Ruffalo & Thompson, 1982). This may sometimes be clinically important. For example plasma theophylline levels have been reported to increase into the toxic range when cimetidine is taken concurrently. In contrast ranitidine does not appear to influence theophylline pharmacokinetics (Dal Negro *et al.*, 1985). It has also been suggested that nifedipine levels are considerably increased in the presence of cimetidine and that this causes a pharmacodynamic effect in hypertensive patients, the combination producing a significantly greater reduction in blood pressure than nifedipine alone (Kirch *et al.*, 1983). Ranitidine at a dose of 150 mg taken with nifedipine does not appear to share this effect (Kirch *et al.*, 1983), although the same group subsequently reported a 71% increase in peak plasma nifedipine concentration

($P > 0.05$) and a 20% increase in the AUC ($P < 0.05$) in six subjects using a higher dose of ranitidine (Kirch *et al.*, 1984). It is unclear whether the effect of ranitidine is real or due to chance since in the second study the treatments do not appear to have been randomised.

We have studied the effects of chronic dosing with cimetidine and ranitidine on nifedipine pharmacokinetics, both after a single dose and at steady state, using a single-blind cross-over protocol in 12 subjects. The aim was to determine whether, on the basis of pharmacokinetic data, there is any advantage in using a particular H₂-receptor antagonist when nifedipine is being prescribed concurrently.

Methods

Subjects

Twelve volunteers were recruited to both parts of the study. They were aged between 18 and 40

years and were within 20% of their ideal body weight. The nature and purpose of the investigation was explained in detail, they were clinically assessed and blood was taken for routine haematological and biochemical screening. Any relevant abnormality or the use of other medication precluded participation. Suitable volunteers were then asked to sign a consent form in the presence of a witness. The protocol was approved by the Central Birmingham Health District Research Ethics Committee.

Study design

a. Single dose nifedipine study There were three separate treatment periods, each lasting 5 days and separated by a 7 day washout period. The three treatments were cimetidine, 800 mg daily at 08.00 h, ranitidine 300 mg at 08.00 h, and placebo tablets 1 daily at 08.00 h. Treatments were given according to a Latin square design. On day 5 of each treatment period volunteers attended in a fasting state for the pharmacokinetic study having taken their cimetidine, ranitidine, or placebo as usual at 08.00 h with 100 ml cold water. On arrival a cannula was inserted into a suitable forearm vein and clotting was prevented by intermittent injection of heparinised saline. This cannula was used for blood sampling after discarding the initial 2 ml of each aspirate. Nifedipine 20 mg in capsule form was given at 09.00 h with 100 ml of cold water. Ten ml blood samples were collected before and then 0.5, 1, 1.5, 2, 3, 4, 6, 8 and 12 h post dosing into lithium heparin tubes, care being taken to keep exposure to light to a minimum. Samples were stored at -20°C until assayed for nifedipine.

b. Chronic dose nifedipine study The design of this study was similar to the single dose nifedipine study except that in addition to treatment with cimetidine 800 mg daily, ranitidine 300 mg daily or placebo 1 tablet daily, nifedipine in capsule form was taken concurrently at a dose of 10 mg at 09.00 h, 16.00 h and 22.00 h during each treatment period. The final dose of nifedipine 10 mg was given at 09.00 h on day 5 of each treatment. Cannulation and blood sampling was the same as for the single dose study.

Nifedipine assay

The method used was specific for unmetabolised nifedipine as described by Rosseel & Bogaert (1983) but using electron-capture detection. Although the oxidized metabolite was seen on the chromatograms, it was not quantitated. Under the conditions described, injections of

spiked samples containing nifedipine showed no conversion to the oxidized metabolite. Nitrendipine (25 ng) was added to 1 ml of plasma as an internal standard followed by 0.5 ml of 0.1 M sodium hydroxide and 1 ml of toluene. The mixture was shaken for 10 min, centrifuged for 10 min at 500 g and the organic phase removed and evaporated to dryness under a stream of nitrogen during application of heat (60°C). A further 1 ml of toluene was added to the aqueous phase and the procedure repeated. The nifedipine extract was reconstituted in 0.1 ml of toluene and 1 μl aliquots injected. The gas chromatograph (Carlo Erba Strumentazione, Model HRGC 5160) was fitted with a cold on-column injector and a 25 mm $\times$ 0.32 mm i.d. fused silica column. The stationary phase was a cross-linked methyl silicone (CP Sil 5CB, Chrompack U.K. Ltd) with a film thickness of 0.12 μm . Following injection the column was programmed for 120–250 $^{\circ}\text{C}$ at a rate of 49.9 $^{\circ}\text{C min}^{-1}$ then to 315 $^{\circ}\text{C}$ at 10 $^{\circ}\text{C min}^{-1}$. Helium was used as the carrier gas at a flow rate of 3 ml min^{-1} and an argon:methane mixture (95:5) was used as a make-up gas at a rate of 30 ml min^{-1} . Electron-capture detection was used and, under the above conditions, nifedipine and nitrendipine had retention times of 5.8 and 6.7 min respectively. The minimum amount of nifedipine detected under these conditions was 1 ng ml^{-1} of plasma. Under the conditions described above, the coefficient of variation of the assay at 7.5 and 75 ng ml^{-1} was 6.3 and 5.5% respectively.

Statistical methods

For each concentration-time curve in the single dose nifedipine study the peak concentration (C_{max}), time to peak (t_{max}) and area under the curve (AUC) between dosing and 12 h were determined. Similar parameters for each steady state concentration-time curve in the chronic dose nifedipine study were obtained except that the AUC for one dose interval (0–8 h) was used. AUC was calculated by the trapezoidal method.

C_{max} and AUC were analysed using analysis of variance allowing for effects due to subjects and treatments. Because there is a relationship between the size of the serum concentration and the variation associated with it, peak and area under the curve were transformed into a logarithmic scale for analysis of variance to be performed on log (peak) and log (AUC). Tukey's test was used to compare placebo, ranitidine and cimetidine pharmacokinetic parameters whenever treatment effects were significantly different. 95% confidence intervals for population treatment means were obtained using Student's

t-distribution percentage points. Times-to-peak were analysed using Friedman's two-way analysis of variance.

Results

a. Single dose nifedipine study

The concentration-time curve for nifedipine following administration of a single 20 mg dose at time 0 after chronic dosing with either cimetidine, ranitidine or placebo are shown in Figure 1. There was no significant difference between the three mean peak serum concentrations, nor between the median times to peak (Table 1). However the mean area under the nifedipine concentration curve (0–12 h) for cimetidine was significantly higher than those for placebo and ranitidine ($P < 0.05$). There was no evidence of a difference in AUC for ranitidine and placebo (Table 1).

b. Chronic dose nifedipine study

The concentration-time curves for nifedipine after chronic dosing for 5 days, the final 10 mg dose being taken at time 0, in combination with either cimetidine, ranitidine or placebo are shown in Figure 2. The peak nifedipine concentration was significantly greater in the presence of cimetidine compared to placebo ($P < 0.05$) but there was no difference in the peak concentration in the presence of ranitidine compared to placebo (Table 2). There was no significant difference between the median times to peak concentration. However the mean area under the steady state nifedipine concentration-time curve (0–8 h) for cimetidine was significantly higher

Figure 1 Concentration-time profile for nifedipine (20 mg orally) after 5 days treatment with ranitidine (300 mg, ■), cimetidine (800 mg, ●) or placebo (▲). Treatments were randomised according to a Latin Square design. Each point is the mean ($\pm$ s.e. mean) of 12 volunteers.

than those for placebo and ranitidine. There was no evidence of a difference in AUC for ranitidine and placebo (Table 2).

Table 1 Pharmacokinetic measurements for nifedipine—single dose study

Treatment	$t_{\max}$ (h)	$C_{\max}$ (95% CI) (ng ml ⁻¹)	AUC (95% CI) (ng ml ⁻¹ h)
Placebo	0.50	131.8 (97.0, 179.0)	366.1 (322.5, 415.7)
Ranitidine	0.75	177.9 (130.9, 241.6)	439.7 (387.2, 499.2)
Cimetidine	0.50	218.1 (160.6, 296.3)	*649.4 (571.9, 737.3)

where $C_{\max}$ = geometric mean peak concentration

$t_{\max}$ = median time to peak

AUC = geometric mean area under nifedipine concentration curves

CI = confidence intervals

* $P < 0.05$ P vs C.; R vs C

Table 2 Pharmacokinetic measurements for nifedipine—chronic dose study

Treatment	$t_{\max}$ (h)	$C_{\max}$ (95% CI) (ng ml ⁻¹)	AUC (95% CI) (ng ml ⁻¹ h)
Placebo	0.5	56.0 (42.1, 74.6)	134.0 (113.4, 158.4)
Ranitidine	1.0	77.7 (58.4, 103.4)	157.0 (132.8, 185.7)
Cimetidine	0.5	*93.4 (70.2, 124.3)	**257.8 (218.0, 304.7)

where $C_{\max}$ = geometric mean peak concentration

$t_{\max}$ = median time to peak

AUC = geometric mean area under nifedipine concentration curves

CI = confidence intervals

* $P < 0.05$ P vs C; R vs C, NS

** $P < 0.05$ P vs C and R vs C

Figure 2 Concentration-time profile for steady state nifedipine (10 mg three times daily) for 5 days together with ranitidine (300 mg, ■), cimetidine (800 mg, ●), or placebo (▲). Details as in Figure 1.

Discussion

In the present study the pharmacokinetics of nifedipine were altered by concomitant treatment with cimetidine. The area under the nifedipine concentration-time curve was substantially increased compared to placebo both after a single dose of nifedipine (77% increase) and under steady state conditions (92% increase). The peak steady state nifedipine concentration was also significantly greater (67% increase) than

with placebo. These results indicate that cimetidine increases the bioavailability of nifedipine. Ranitidine produced a small increase in the $C_{\max}$ and AUC for nifedipine compared to placebo, but this did not reach statistical significance.

There are several ways in which H_2 -receptor antagonists might affect the pharmacokinetics of other drugs. These include changes in gastric absorption due to reduction in acidity, and an inhibition of liver enzyme function (Powell & Donn, 1984). The liver cytochrome P-450 mixed function oxidase system is inhibited by cimetidine but not by ranitidine which does not possess cimetidine's imidazole ring thought to be the site of binding to cytochrome P-450 (Bell *et al.*, 1981; Gerber *et al.*, 1985). Nifedipine is extensively metabolised in the liver by oxidation and hydroxylation (Kleinbloesem *et al.*, 1984) and any inhibition of the oxidative pathway by cimetidine would be expected to increase plasma concentrations of nifedipine as was found in both parts of the present study. Changes in gastric pH by ranitidine have been suggested as responsible for increased absorption of nifedipine (Adams *et al.*, 1986) but our results do not support any influence of gastric acidity on nifedipine which is almost completely absorbed (Raemisch & Sommer, 1983). A potentiation of the hypotensive effect of nifedipine in the presence of cimetidine has been reported, a response not seen with ranitidine (Kirch *et al.*, 1983). This suggests that the cimetidine-induced changes in nifedipine pharmacokinetics can be translated into clinically important pharmacodynamic responses. This may be particularly relevant with the recent introduction of the large single daily dose of cimetidine 800 mg. Ranitidine 300 mg, now advocated for the treatment of duodenal ulcer disease should however not affect nifedipine plasma concentrations when the two are co-

prescribed. Thus when it is necessary to prescribe an H_2 -receptor antagonist for a patient

already taking nifedipine it would seem advisable to use ranitidine in preference to cimetidine.

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