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The pharmacokinetics and pharmacodynamics of nifedipine at steady state during concomitant administration of cimetidine or high dose ranitidine

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Ranitidine may be used at doses of up to 300 mg twice daily in the healing of duodenal ulcers, and this study investigated the potential for a pharmacokinetic or pharmacodynamic interaction between nifedipine 10 mg three times daily and ranitidine 300 mg twice daily compared with cimetidine 800 mg daily and placebo in a randomised crossover study in 18 healthy male subjects. Twelve blood samples were taken on the fifth day in each treatment period and assayed for nifedipine by h.p.l.c. Pulse, blood pressure and ECG recordings were also taken. Cimetidine, but not ranitidine, produced significant changes in the pharmacokinetics of nifedipine at steady state. Mean ± s.d. values of AUC were 105 ± 40 $\mu g\,l^{-1}$ h for placebo treatment, 111 ± 45 $\mu g\,l^{-1}$ h for ranitidine and 211 ± 64 $\mu g\,l^{-1}$ h for cimetidine ($P < 0.001$), and C_{max} values were 33 ± 14, 39 ± 27 and 76 ± 40 $\mu g\,l^{-1}$ ($P < 0.001$), respectively. Neither ranitidine nor cimetidine produced statistically significant changes in the pharmacological response to nifedipine.

Keywords nifedipine ranitidine cimetidine pharmacokinetics pharmacodynamics

Introduction

Several studies have compared the effects of cimetidine and ranitidine, in doses up to 150 mg three times daily, on the pharmacokinetics and pharmacodynamics of nifedipine (Kirch *et al.*, 1983; Renwick *et al.*, 1987; Schwartz *et al.*, 1988; Smith *et al.*, 1987). These studies showed a statistically significant increase in the area under the plasma concentration-time curve (AUC) for nifedipine during concomitant cimetidine therapy but not during concomitant ranitidine therapy. Kirch *et al.* (1983) argued that their initial study had used too low a dose of ranitidine (150 mg) and carried out a further study in seven subjects using ranitidine 300 mg at night and nifedipine 20 mg three times daily. In this study they reported a significant ($P < 0.05$) increase in the nifedipine AUC in the absence of any change in pharmacodynamic response (Kirch *et al.*, 1984).

Recent multicentre clinical trials have shown that treatment of duodenal ulcer disease with ranitidine 300 mg twice daily results in significantly higher healing rates than standard doses (Butruk *et al.*, 1989; Dobrilla & De Pretis, 1989), hence providing an alternative dosage option. It is therefore important, in the light of Kirch *et al.* (1984) observations, to investigate the potential for an interaction between nifedipine and this higher dose of ranitidine.

Methods

Design

The study was a three-way randomised crossover with each treatment period being separated by a 1 week washout. Cimetidine was included as a positive control. The three treatments were nifedipine 10 mg three times daily for 4 days and nifedipine 10 mg in the morning on the fifth day plus ranitidine 300 mg twice daily, cimetidine 800 mg in the morning and placebo at night or placebo twice daily for 4 days and a single dose on the morning of the fifth day.

Ethical aspects

Ethics committee approval was obtained in writing from an independent, voluntary committee prior to the start of the study. All subjects gave written informed consent

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before participating in the study. The study was performed in accordance with the guidelines of the Declaration of Helsinki on biomedical research involving human subjects (Venice revision 1983).

Subjects

The subjects included 18 healthy non-smoking male volunteers. Subjects were excluded if clinically relevant abnormal haematology or biochemistry was found, if the pre-study blood pressure was below 100/55 mm Hg, or if orthostatic hypotension was observed.

Clinical procedures

Subjects were resident within the Clinical Unit from 22.00 h on day 4 until the final blood sample on day 5. Blood sampling and drug administration at other times were done on an out-patient basis. On the morning of day 5 the subjects remained in bed until 4 h post-dosing.

The subjects were fasted from 22.00 h on day 4 until the morning of day 5, when they were given a light breakfast. A light lunch was given 4 h post-dosing on day 5. At other times subjects were allowed to continue their normal diet. Restrictions on caffeine and alcohol intake were imposed on day 4 until the last sample on day 5.

Each subject's pulse, blood pressure and ECG recording were noted immediately prior to the morning dose on days 2, 3, 4 and 5 and at 1.5, 2.5, 4 and 8 h post-dosing on day 5. Duplicate readings of pulse and blood pressure were made, separated by at least 1 min.

Blood samples (10 ml) for nifedipine assay were taken immediately prior to dosing and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8 and 10 h after dosing with nifedipine on day 5. Since nifedipine is sensitive to ultraviolet light, all blood sampling was carried out under artificial sodium lighting. Samples were placed in plastic tubes containing lithium heparin, centrifuged at 600 *g* for 10 min, and the plasma was removed and stored in the dark at −20° C to await analysis.

Sample analysis

Plasma nifedipine concentrations were measured using a specific, validated reversed phase h.p.l.c. assay based on the method of Kleinbloesem *et al.* (1984). The assay was run using an HP 1090 dual pump LC system, an HP 3392 reporting integrator, and a Kratos Spectroflow 773 absorbance detector set at 236 nm. A 150 × 4.6 mm ODS2 3μ Spherisorb analytical column was used giving an elution time of 17 min.

Calibration curves comprising triplicates of six concentrations (5–100 $\mu g\, l^{-1}$, precision 0.7–9.0%), and quality control samples comprising three concentrations in duplicate, were included in each analytical run.

Data analysis

Values for standard pharmacokinetic parameters were calculated for nifedipine within one inter-dosing interval by compartmental model independent means using the Siphar software package (release 3.3, Simed, Créteil, France). The parameters included the terminal half-life ($t_{½}$), the area under the plasma drug concentration-time curve (AUC), the oral clearance (CL/*F*), and the apparent volume of distribution (V_z/F).

Pharmacodynamic results are reported as weighted averages and as the maximum (or minimum) change. The baseline for each physiological parameter was defined as the average of the final two results obtained prior to the final nifedipine dose.

The effects of ranitidine and cimetidine on the pharmacokinetics and pharmacodynamics of nifedipine were assessed using an ANOVA incorporating the factors subject, treatment and period. A test for treatment by period interaction was carried out using the procedure REGRESSION in SPSS.

Results

Clinical

The 18 subjects had a mean age of 22 years (range 19–35 years). Seventeen subjects completed the study, one being withdrawn during the final period owing to influenza. One subject suffered recurrent insomnia, headaches and palpitations in all three study periods and nifedipine was thought to be the cause of these symptoms. The only other adverse event reported was abdominal pain in one subject. No clinically relevant abnormalities in haematology or biochemistry were found post-study.

Pharmacokinetics

The arithmetic means of each of the parameters defining the pharmacokinetics of nifedipine at steady state are shown in Table 1. After the final dose of nifedipine, maximum plasma drug concentrations were achieved within 0.5 to 5 h of dosing. Thereafter elimination was rapid with plasma drug concentration falling below the limit of assay in < 10 h.

Ranitidine 300 mg twice daily produced no significant changes in the pharmacokinetics of nifedipine at steady state, the 90% confidence intervals associated with the comparison of C_{max} and AUC for the placebo and ranitidine phases being within the limits of 0.8–1.2 for AUC (0.85–1.14) but just outside for C_{max} (0.8–1.31) (Pabst & Jaeger, 1990). In contrast, cimetidine 800 mg in the morning produced a 128% increase in C_{max} and an approximately 100% increase in AUC. The effect of cimetidine on CL/*F* and V_z/F was similar, producing a 46% decrease in both parameters but no significant change in the terminal half-life of nifedipine (Table 1). In contrast, ranitidine coadministration resulted in negligible changes in nifedipine pharmacokinetics.

Pharmacodynamics

Neither ranitidine nor cimetidine produced statistically significant changes in the pharmacological responses to nifedipine (Figures 1a–d).

Nifedipine produced an initial rise in mean pulse rate which reached a maximum approximately 1–2 h after dosing (Figure 1a). The mean P-R interval shortened by

Table 1 Arithmetic mean of the pharmacokinetic parameters for nifedipine at steady state during administration of placebo, ranitidine 300 mg twice daily or cimetidine 800 mg once daily in 18 healthy male subjects

Parameter	*Placebo*	*Ranitidine*	*Cimetidine*	*Statistics*
C_{max} ± s.d. ($\mu g\ l^{-1}$)	33 ± 14	39 ± 27	76 ± 40	$P < 0.001$
t_{max} (h)*	2.03 0.50–4.06	2.01 0.50–5.04	1.99 0.50–3.01	
AUC ± s.d. ($\mu g\ l^{-1}\ h$)	105 ± 40	111 ± 45	211 ± 64	$P < 0.001$
$t_{½}$ ± s.d. (h)	2.02 ± 0.89	1.82 ± 0.73	2.26 ± 0.51	$P = 0.05$
CL/F ± s.d. ($l\ h^{-1}$)	111 ± 54	107 ± 49	62 ± 16	$P < 0.001$
V_z/F ± s.d. (l)	304 ± 140	258 ± 128	165 ± 52.4	$P < 0.001$

*Median and range.

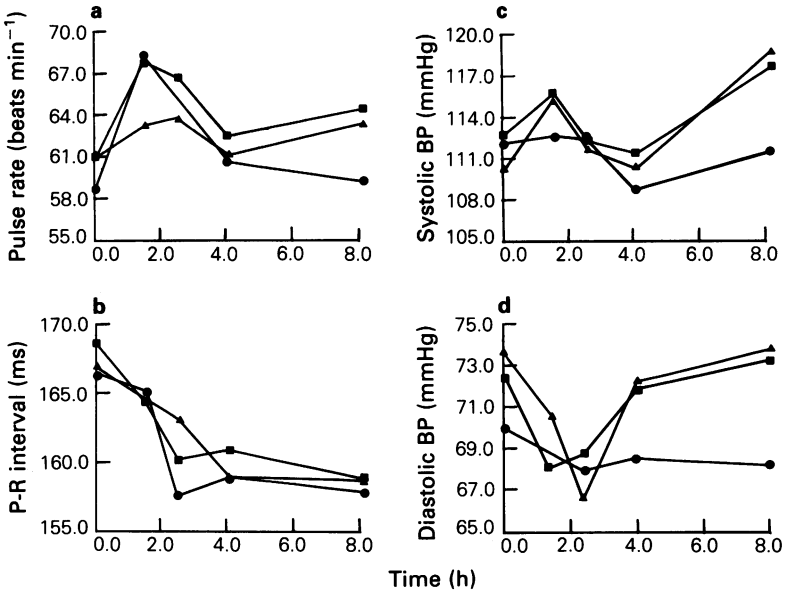

Figure 1 Mean pharmacodynamic responses associated with the final 8 h interdosing interval of nifedipine in the presence of ranitidine (▲), placebo (■) and cimetidine (●).

up to 10 ms during the 8 h observation period (Figure 1b). The effects of nifedipine on the systolic blood pressure are shown in Figure 1c. Nifedipine had a more pronounced effect on diastolic blood pressure producing a reduction which was maximal at about 2 h after dosing, thus coinciding with the average C_{max}. Whilst ranitidine exerted no apparent effect on diastolic blood pressure, concomitant cimetidine therapy resulted in low pressure throughout the dosing interval (Figure 1d).

Discussion

Ranitidine 300 mg twice daily produced no effects on the steady-state pharmacokinetics of nifedipine or on the ensuing pharmacological response. In contrast, the effects of cimetidine on the pharmacokinetics were marked and in agreement with previous studies (Kirch *et al.*, 1983; Renwick *et al.*, 1987; Schwartz *et al.*, 1988; Smith *et al.*, 1987).

Nifedipine, being a drug with a high hepatic extraction ratio, has a low oral bioavailability. Consequently concomitantly administered drugs such as cimetidine, which may potentially inhibit the metabolism of nifedipine, may be expected to produce an increase in oral availability of this agent due to inhibition of the enzymes responsible for the first-pass metabolic loss. This effect was suggested by the fact that there were similar decreases in the apparent clearance (CL/F) and the apparent volume of distribution (V_z/F), most probably as a consequence of an increase in availability produced by concomitant cimetidine administration.

The marked increase in circulating plasma nifedipine concentrations during cimetidine administration did not translate into a statistically significant potentiation of pharmacological activity.

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