Effect of indomethacin on the pharmacokinetics and pharmacodynamics of felodipine

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1 We studied the effects of pre-treatment with oral indomethacin (25 mg four times daily for 3 days) on the pharmacokinetics, haemodynamics and diuretic properties of oral felodipine (10 mg single dose) in 12 healthy male volunteers using a placebo controlled double-blind four-way crossover protocol.

2 Felodipine with or without indomethacin pretreatment reduced standing diastolic blood pressure ($P < 0.001$) at 0.5 to 3.0 h after dosing compared with placebo or indomethacin alone. Systolic blood pressures during indomethacin treatment alone were consistently higher than the other three treatment groups ($P < 0.01$), presumably due to sodium and fluid retention.

3 Felodipine and felodipine plus indomethacin produced significantly greater excretion of urine and urinary sodium, but not of urinary potassium or creatinine when compared with placebo ($P < 0.01$) over an 8 h period.

4 The pharmacokinetic parameters of felodipine ($C_{\max}$, $t_{\max}$, $t_{1/2}$ and AUC), the concentration-response curves for blood pressure lowering effects, the reflex tachycardia, diuretic properties and side-effects profile of felodipine were not significantly altered by indomethacin pretreatment in normal volunteers.

Keywords felodipine indomethacin pharmacodynamics pharmacokinetics

Introduction

Felodipine is a calcium channel blocker of potential use in the treatment of essential hypertension (Mace *et al.*, 1985) and chronic stable angina (Sheridan *et al.*, 1987). The drug exerts its effect, in part, by arteriolar vasodilation which is frequently associated with reflex sympathetic activation (Rönn *et al.*, 1985). Fluid retention is a common sequela of vasodilator therapy, although felodipine has been shown to have mild diuretic properties (Sluiter *et al.*, 1985; Katzman *et al.*, 1986) which may offset this adverse effect.

Previous studies have demonstrated that indomethacin is capable of attenuating the natriuretic effect of diuretics such as frusemide and thiazides

(Steiness & Waldorff, 1982). This interaction is thought to be mediated by prostaglandins which are known to affect blood pressure, serum electrolytes and fluid balance (Sullivan, 1982). In addition, evidence suggests that nonsteroidal anti-inflammatory drugs are capable of reducing liver blood flow (Feely & Wood, 1983). This potentially could result in the altered disposition of high hepatic clearance drugs such as felodipine (Edgar *et al.*, 1985).

The objective of the present study was to investigate the effect of indomethacin pretreatment on the pharmacokinetics and pharmacodynamics of felodipine in healthy male subjects.

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Methods

A four-way crossover double-blind placebo-controlled trial was conducted in 12 healthy male volunteers, randomized according to a Latin square design. The subjects, aged 22–39 years, weight 69–92 kg, gave written informed consent to the procedures which had been explained to them. The protocol was approved by the Institutional Review Committees. Prestudy subject evaluation consisted of a medical history, a physical examination, ECG, haematology, biochemistry and urinalysis screen. Subjects were placed on a standard diet, containing 115 mEq sodium daily, for 3 days before and during the period of the study. For 3 days, subjects received either indomethacin 25 mg or matching placebo four times daily. On the fourth day, the volunteers received, in addition, a single oral dose of felodipine 10 mg or matching placebo. An indwelling catheter was inserted in a forearm vein and a total of 14 blood samples were collected at 0, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 7, 8, 10, 12 and 24 h following the administration of felodipine or placebo on the study days.

Supine and standing blood pressures were measured in duplicate at all plasma collection time points using a Hawksley random zero sphygmomanometer with diastolic pressure taken at the fifth Korotkoff sound. At each observation, the subjects were supine for 15 min, and standing for 3 min. Heart rate was measured in duplicate at the end of these periods in the supine and standing positions. In addition, urine aliquots were collected at 0–4, 4–8, 8–12 and 12–24 h for measurement of creatinine, sodium and potassium renal clearances and fractional urinary excretion.

The study was conducted on four occasions according to design, each study day being separated by at least 10 days. Side-effects were volunteered or obtained by open questioning throughout the 4 week trial.

The drugs used in this study comprised felodipine 10 mg tablets and matching placebos (Astra, AB Hässle, Mölndal, Sweden) and indomethacin 25 mg capsules and matching placebos (Indocid®-Merck Sharp and Dohme).

The concentration of felodipine in plasma samples was measured by gas chromatography with electron capture detection. The assay had a coefficient of variation of 4% at 25 nmol l⁻¹ and 10% of 2 nmol l⁻¹ (Ahnoff, 1984).

Pharmacokinetic analysis was performed by

fitting the data by a first order absorption and first order elimination open model using a non-linear extended least squares regression program (MK Model). The area under the plasma drug concentration-time curve (AUC) was calculated using the Lagrange technique, either alone or in conjunction with log-trapezoidal techniques (Yeh & Kwan, 1978). Since sampling around the peak was frequent, the highest value in the plasma drug concentration profile was taken as the peak concentration, designated ($C_{\max}$). The time to reach this peak concentration was denoted $t_{\max}$. The half-life ($t_{1/2}$) was determined by log-linear regression of the terminal slope of the plasma drug concentration-time profile.

Pharmacodynamic analysis included comparisons of supine and diastolic blood pressures and heart rates at all blood collection time points among the four treatment groups. Similarly, renal sodium, potassium and creatinine clearances were compared using the fractional urine collections for all four treatment groups.

The haemodynamic effects of felodipine with and without indomethacin were fitted by concentration-response models using an extended nonparametric pharmacokinetic-pharmacodynamic technique (Unadkat *et al.*, 1986). Haemodynamic responses were reported as a ratio of treatment to baseline (placebo) at all corresponding time points. The fit criterion for the estimate of the pharmacodynamic model (linear, $E_{\max}$ or sigmoid $E_{\max}$) was based on the Schwarz criterion (Schwarz, 1978) and graphical analysis (MK Model). Pharmacodynamic parameters were calculated for the mode of best fit and the values compared statistically for felodipine with and without indomethacin. Results are presented as the mean $\pm$ s.e. mean and comparisons were made by analysis of variance for repeat measures. When a probability level of < 0.05 was observed, comparisons between treatment groups were made using the paired Student's *t*-test or Wilcoxon signed-ranks tests, where applicable.

Results

Pharmacokinetics

The mean plasma felodipine concentration-time profiles for the subjects are illustrated in Figure 1. The individual pharmacokinetic estimates for the 12 adult male volunteers receiving felodipine with or without indomethacin are shown in Table 1. No significant differences were evident.

Haemodynamics

Supine and standing blood pressures and heart rate were compared among the four treatment

Table 1 Pharmacokinetics (mean $\pm$ s.e. mean) of felodipine in 12 normal volunteers, with and without indomethacin treatment (25 mg four times daily for 3 days)

	Felodipine	Felodipine-Indomethacin
Peak plasma concentration (nmol l ⁻¹)	14.5 $\pm$ 2.2	16.5 $\pm$ 2.2
Time to peak (h)	1.6 $\pm$ 0.3	1.4 $\pm$ 0.2
Elimination half-life (h)	3.2 $\pm$ 0.3	2.4 $\pm$ 0.1
Area under the curve (nmol-h l ⁻¹)	65 $\pm$ 10	58 $\pm$ 8

Felodipine-Indomethacin values were not significantly different from felodipine alone.

Figure 1 Plasma felodipine concentration-time profile for the mean ($\pm$ s.e. mean) data obtained after oral felodipine 10 mg with ($\square$) or without ($\bullet$) indomethacin pretreatment, 25 mg four times daily for 3 days, in 12 healthy male volunteers. **Figure 2** Mean (s.e. mean) standing diastolic blood pressures for the four treatment groups over the study days. Treatment groups included placebo ($\bullet$), indomethacin ($\blacksquare$), felodipine ($\circ$), and felodipine plus indomethacin ($\square$). Values for both felodipine groups were significantly lower than placebo or indomethacin alone at 0.5 to 3.0 h after dosing ($P < 0.05$).

groups. Systolic blood pressures during indomethacin treatment alone were consistently higher than the other three treatment groups during the study days. Standing diastolic blood pressures for both felodipine study periods were significantly ($P < 0.05$) lower than placebo and indomethacin alone between 0.5 to 3.0 h after dosing (Figure 2), and heart rate was elevated (Figure 3). Indomethacin did not alter the haemodynamic effects of felodipine. This was shown by ANOVA comparison of blood pressure and heart rate data between the two felodipine groups (with and without indomethacin) at all time points and examination of the calculated mean pharmacodynamic parameters for the two groups. A representative hysteresis loop of the haemodynamic data is shown in Figure 4 for the mean standing heart rate ratio (treatment/placebo) vs plasma felodipine concentration. The loop area was minimized by the extended nonparametric method and the final estimated effect curve derived from the mean of the two hysteresis

Figure 3 Mean ($\pm$ s.e. mean) standing heart rates for the four treatment groups over the study days. Treatment groups included placebo ($\bullet$), indomethacin ($\blacksquare$), felodipine ($\circ$) and felodipine plus indomethacin ($\square$). Values for felodipine group were elevated compared with placebo or indomethacin alone ($P < 0.05$).

Figure 4 Mean ($\pm$ s.e. mean) standing heart rate ratio (treatment/placebo) vs plasma felodipine concentration hysteresis loops for felodipine ($\bullet$) and felodipine plus indomethacin ($\square$).

limb points at all effect compartment concentrations. The pharmacodynamic model that most adequately described the haemodynamic effects of blood pressure and heart rate ratios vs effect compartment concentrations, as discriminated by the Schwarz criterion, was the linear model. The pharmacodynamic parameters of slopes and intercepts were compared statistically for the two felodipine groups. For example, parameters were estimated from the best fit of the standing heart rate vs felodipine effect compartment concentration to the linear pharmacodynamic model. The mean ($\pm$ s.e. mean) slopes (0.013 ± 0.002 vs 0.014 ± 0.003 l nmol⁻¹) and intercepts (0.975 ± 0.163 vs 1.030 ± 0.124) for felodipine with and without indomethacin, respectively, were not statistically different. Similarly, no differences were observed in the pharmacodynamic parameters for the two felodipine groups (with or without indomethacin) for any of the haemodynamic endpoints analyzed, including: supine and standing systolic and diastolic blood pressure and heart rate.

Urinary electrolyte excretion

For the urine collection periods of 0–4 and 0–8 h, felodipine with or without indomethacin produced a significantly greater excretion of urine (Table 2) and sodium (Figure 5), but not potassium or creatinine when compared with placebo. Similarly, the fractional excretion of sodium from 0–4 h was significantly higher during both

Table 2 Fractional excretion and excretion rates of urinary electrolytes over 0–4 h post-dose (mean $\pm$ s.e. mean)

	Placebo	Felodipine alone	Indomethacin	Felodipine-indomethacin
Creatinine clearance (ml min ⁻¹)	131 $\pm$ 39	131 $\pm$ 54	150 $\pm$ 95	140 $\pm$ 47
Urine volume (ml)	212 $\pm$ 98	290 $\pm$ 160*	258 $\pm$ 122	418 $\pm$ 221*
Sodium excretion rate (μ mol min ⁻¹)	85 $\pm$ 33	134 $\pm$ 67*	109 $\pm$ 47	193 $\pm$ 128*
Potassium excretion rate (μ mol min ⁻¹)	80 $\pm$ 37	64 $\pm$ 19	80 $\pm$ 31	84 $\pm$ 32
Fractional sodium excretion (%)	0.47 $\pm$ 0.19	0.73 $\pm$ 0.29*	0.61 $\pm$ 0.28	0.92 $\pm$ 0.47*
Fractional potassium excretion (%)	13.9 $\pm$ 4.7	12.7 $\pm$ 3.6	14.6 $\pm$ 7.8	15.2 $\pm$ 5.5

*Values are significantly different from placebo ($P < 0.05$)

Figure 5 Mean (s.e. mean) sodium excretion for the four treatment groups over the study days. Treatment groups included: placebo (■), indomethacin (□), felodipine (▨), and felodipine plus indomethacin (▩). The excretion of sodium from 0–4 h was significantly higher during both felodipine treatments (*) compared with placebo ($P < 0.05$)

felodipine treatments compared with placebo. Sodium excretions were highest when subjects were pretreated with indomethacin. These changes occurred without changes in creatinine clearance (Table 2). Overall, indomethacin pretreatment did not diminish the diuretic or natriuretic effects of felodipine.

Adverse effects

A total of 34 adverse effects were reported by 10 of the 12 subjects. None was reported when subjects received placebo. The side effects reported with felodipine alone were headache (6) and flushing (3); for indomethacin alone were headache (4), lightheadedness (4) and gastrointestinal complaints (3); and for the combination included headache (5), lightheadedness (4), dizziness (2), gastrointestinal complaints (2) and weakness (1).

Discussion

Indomethacin appeared to have no discernible effects on the pharmacokinetic or pharmacodynamic parameters of felodipine. Changes in blood pressure and heart rate were as expected for an arterial vasodilator; namely, a decrease in blood pressure and transient compensatory increase in heart rate. The blood pressure decrease was only significant for diastolic blood pressure. The effect on heart rate was of slightly longer duration, presumably representing the ability

of the increased heart rate and resultant cardiac output increment to compensate for any decrease in peripheral resistance at the later observation times. However, with chronic dosing in hypertensive patients, felodipine has been shown to maintain decreases in blood pressure while heart rate returns to normal (Smith *et al.*, 1986). In the present study, the acute haemodynamic changes were not significantly modified by indomethacin pretreatment. This is evident by the observation that these parameters did not differ between felodipine, with and without indomethacin pretreatment at any time point. In addition, no apparent shift in the concentration-response curves occurred for any of the haemodynamic endpoints when indomethacin was added, as suggested by statistically comparable slopes and intercepts for the pharmacodynamic plots.

The renal effects of felodipine were apparently selective for urine volume and sodium excretion since potassium and creatinine were not significantly affected. However, there was a 15% rise in mean creatinine clearance with indomethacin (Table 2) compared with placebo, although this failed to achieve statistical significance. Both felodipine treatment groups demonstrated similar responses during the 8 h after dosing when plasma concentrations of felodipine were highest. The natriuretic effects of felodipine were not blunted by indomethacin pretreatment. In fact, the diuretic properties of felodipine were most noticeable after subjects presumably had indomethacin-induced sodium and fluid retention. The results of this study are consistent with animal experiments which showed inhibition of sodium and water reabsorption in the distal tubule and collecting duct while potassium excretion was unaffected (DiBona, 1985).

The side-effects for felodipine (headache, flushing) and indomethacin (headache, gastrointestinal complaints) were frequent compared with placebo. This is consistent with observations in clinical trials where minor adverse effects from felodipine can be experienced in a relatively high percentage of a study population (Maclean *et al.*, 1986). However, indomethacin appeared to diminish the flushing effect of felodipine. This is consistent with the hypothesis that prostaglandins may play a role in cutaneous flushing (Wilkin, 1981).

In summary, indomethacin did not significantly alter the pharmacokinetics, blood pressure lowering effects, reflex tachycardia or diuretic properties of felodipine.

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