Br. J. clin. Pharmac. (1991), **31**, 148–153 ADONIS 0306525191000296

A study of the acute pharmacodynamic interaction of ramipril and felodipine in normotensive subjects

A. D. BAINBRIDGE, R. J. MACFADYEN, K. R. LEES & J. L. REID
University Department of Medicine and Therapeutics, Stobhill General Hospital, Glasgow G21 3UW

1 The possibility of an acute pharmacokinetic or pharmacodynamic interaction between the ACE inhibitor ramipril and the calcium antagonist felodipine was examined in 12 normotensive male volunteers.

2 Ramipril (5 mg) and felodipine ER (10 mg) were administered orally in a double-blind, randomised, placebo-controlled, Latin square design to fasting subjects.

3 There was no evidence of a pharmacokinetic interaction between agents. The concentration-time profiles remained unaltered by coadministration of both agents.

4 Plasma ACE inhibition by ramiprilat was unaffected by concurrent felodipine. The trend towards increased fractional sodium excretion after felodipine was not influenced by ramipril. Plasma renin activity, aldosterone and catecholamines remained unaltered.

5 Combination therapy produced a statistically significant fall in blood pressure supine and erect which was not evident with monotherapy. The reflex tachycardia associated with felodipine monotherapy was significantly attenuated by the coadministration of ramipril.

6 This study presents further evidence for the effective combination of ACE inhibitors and calcium antagonists to lower blood pressure. The reflex tachycardia associated with calcium antagonist therapy can be significantly reduced by coadministration with sustained antihypertensive effect.

Keywords ramipril felodipine ER heart rate response attenuation pharmacodynamic interaction

Introduction

As a prelude to a study in essential hypertension of the utility of a combination of the angiotensin converting enzyme (ACE) inhibitor ramipril (Heber *et al.*, 1988) and an extended release formulation of the calcium antagonist felodipine (Liedholm & Melander, 1989), a study was performed to investigate safety, tolerance and the possible pharmacokinetic and pharmacodynamic interactions of such a combination in normal male subjects.

Dihydropyridine calcium antagonists, in common with other vasodilators, may acutely increase liver blood flow (Meredith *et al.*, 1984). They may thereby alter the pharmacokinetics of other drugs (Pasanisi *et al.*, 1984) or even their own disposition (Meredith *et al.*, 1983).

There has been controversy as to whether the co-administration of an angiotensin converting enzyme (ACE) inhibitor is able to attenuate the reflex tachycardia induced by the acute administration of a dihydropyridine calcium antagonist. The addition of captopril was reported to reduce the acute tachycardia associated with the administration of nifedipine in patients with severe primary hypertension (Guazzi *et al.*, 1984). In normal volunteers the ACE inhibitor benazapril was found to buffer the rise in heart rate caused by a nicardipine infusion (Bellet *et al.*, 1987). However this pattern of response is by no means a consistent finding. No significant buffering of heart rate response was observed when a combination of nicardipine and enalapril was given to essential hypertensives (Donnelly *et al.*, 1987) or the combination of lisinopril and nifedipine to normal volunteers (Lees & Reid, 1988).

Correspondence: Dr R. J. MacFadyen, University Department of Medicine and Therapeutics, Stobhill General Hospital, Glasgow G21 3UW

Methods

Subjects

The study design was approved by the local Ethics Review Committee and written informed consent was obtained. Twelve normotensive male volunteers were recruited following screening for good health by means of history, physical examination, urinalysis, electrocardiograph and routine haematology and biochemistry. The mean age of the volunteers was 29 years (range 22–40), their mean weight was 71.6 kg (range 64–81) and their mean height was 175 cm (range 165–185).

Design

This was a double-blind, four period, crossover study using a Latin square design balanced for carry over effects in 12 subjects. The four treatments, each given as an oral dose with matched placebo where appropriate, at least fourteen days apart: 1) Ramipril 5 mg + placebo felodipine. 2) Felodipine 10 mg + placebo ramipril. 3) Ramipril 5 mg + felodipine 10 mg. 4) Placebo ramipril + placebo felodipine.

At the beginning of each study period, subjects attended the Clinical Pharmacology Research Unit at 08.30 h, having fasted from 22.00 h on the previous night apart from a light liquid breakfast of 100 ml of orange juice. Each subject emptied his bladder and then an antecubital venous cannula (Venflon®) was inserted. After at least 20 min rest in the supine position, the baseline recordings were taken and then the appropriate tablets were given with 200 ml of water. Each recording followed the same sequence: blood pressure and heart rate were recorded by Datascope (Accutorr 2A) semi-automatic sphygmomanometer in triplicate after at least 10 min supine rest, a venous blood sample for drug levels was drawn and then blood pressure and heart rate were recorded after 2 and 5 min standing. The observation times were 0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 10, 12, 24, 48, 72 and 96 h from dosing. Samples for plasma noradrenaline were collected before dosing and after 1, 2, 4, 6, 8, 12 and 24 h. Samples for plasma ACE activity were collected before dosing and after 1, 2, 4, 6, 8, 10, 12, 24 and 48 h. Plasma renin and aldosterone concentrations were measured before dosing and after 4, 6, 8, 12 and 24 h. Aliquots of urine were collected and stored representing the following time periods: 0–2, 2–4, 4–6, 6–8, 8–10, 10–12 and 12–24 h. The subjects were questioned about symptoms at each of the observation times.

Laboratory methods

Ramiprilat Ramiprilat, the active metabolite of ramipril, was assayed by a radioimmunoassay (Eckert *et al.*, 1985). Results are expressed as ng ml^{-1} of plasma. The limit of detection was < 1 ng ml^{-1}. The intra- and inter-assay coefficients of variation ranged from 3 to 14% at 1 to 30 ng ramiprilat ml^{-1}.

Felodipine Felodipine was assayed by gas chromatography (Ahnoff, 1984). Results are expressed as nmol l^{-1} of plasma. The limit of detection was 2 nmol l^{-1}. The inter-assay coefficient of variation was < 4% at 25 nmol l^{-1}.

Plasma angiotensin converting enzyme activity Plasma ACE activity was measured by an h.p.l.c. assisted assay (Chiknas, 1979), for which the inter- and intra-assay coefficients of variation were 3.27% and 1.98% respectively and the limit of detection was 0.5 eu l^{-1}. The normal range for males is 15.3–26.9 eu l^{-1}.

Renin activity Plasma renin activity was measured using an indirect radioimmunoassay which depends on the rate of production of angiotensin I in a standard incubation mixture (Derkx *et al.*, 1979). The inter- and intra-assay coefficients of variation are normally 7.0% and 5.5% respectively with a normal range of 0–12 ngAI ml^{-1} h^{-1}.

Aldosterone A direct radioimmunoassay was used (McKenzie & Clements, 1974). The inter- and intra-assay coefficients of variation were 11.0% and 7.3% respectively.

Noradrenaline Plasma noradrenaline was measured by a catechol-*o*-methyltransferase radioenzymatic method (da Prada & Zurcher, 1976). The inter- and intra-assay coefficients of variation were 15% and 13% respectively. The normal range for noradrenaline is 0.3–7.5 nmol l^{-1}.

Routine laboratory analysis Urinalysis was carried out on freshly voided specimens by dip sticks (Multistix—Ames Laboratories). The haematology measurements were by Coulter Counter and the biochemical analyses were performed on an SMA-C auto-analyser using standard methods.

Data analysis

Pharmacokinetic analysis Model independent methods were used to analyse the concentration time profiles. The area under the concentration time curve from 0–96 h (AUC 0–96), was derived using standard methods (Gibaldi & Perrier, 1982). The study had 80% power of detecting a 20% change in the AUC of ramiprilat.

Statistical methods Repeated measures analysis of variance (RAMOVA) was performed on an ICL 2988 computer using the program Rummage and the Bonferroni method for calculating 95% confidence intervals. Main drug effects and drug–time interactions were tested. Plasma angiotensin converting enzyme activity was converted to percentage ACE inhibition before analysis: % ACE inhibition = 100 (1 − ACE/pretreatment ACE). Plasma renin activity, aldosterone and catecholamines were analysed following logarithmic transformation to normalise their distributions. The adverse event profiles for each phase were analysed by means of Cochran's Q-test. The error bars given in the figures represent one standard deviation. Although these indicate the variability in the raw data they do not portray the repeated measures nature of the study design.

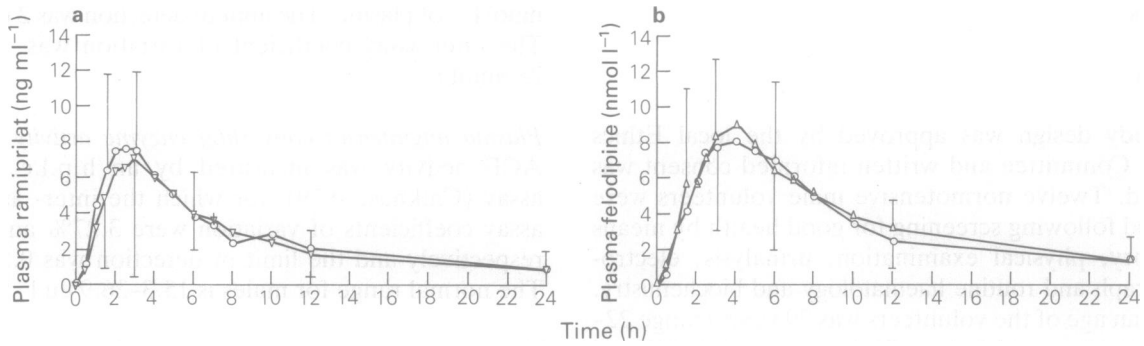

Figure 1 Plasma concentration-time profiles for ramiprilat a) and felodipine b) after oral dosing with ramipril (5 mg) and felodipine ER (10 mg) alone (▽ △) or in combination (○).

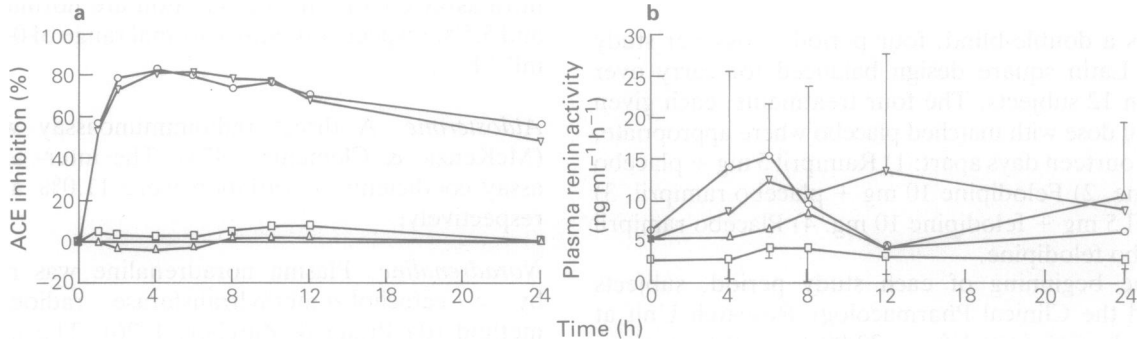

Figure 2 Plasma angiotensin converting enzyme activity a) and renin activity b) after ramipril (▽), felodipine ER (△), combination therapy (○), or placebo (□).

Table 1 The area under the concentration time curve between 0–96 h (AUC; felodipine nmol l^{-1} h; ramiprilat ng ml^{-1} h), peak observed concentration (C_{max}; h) and time to peak observed concentration (t_{max}; h). Mean (s.d.); $n = 11$.

	AUC	C_{max}	t_{max}
Felodipine alone	93.3 (46.6)	11.0 (6.2)	3.5 (1.4)
Felodipine with ramipril	96.4 (92.9)	10.5 (4.8)	4.5 (2.3)
Ramiprilat	66.7 (45.7)	8.8 (5.7)	3.0 (1.8)
Ramiprilat with felodipine	73.1 (58.5)	9.1 (5.8)	2.5 (0.5)

Results

One subject vomited due to an intercurrent illness early on the day when both treatments were given and no ramiprilat was detectable. He subsequently admitted to flu-like symptoms prior to attendance and this was therefore considered to be unrelated to the administration of the drugs. The data from this subject were thus excluded from the analysis.

Adverse events

Headache occurred in 8 out of 11 following the combination of ramipril and felodipine, in 6 out of 11 with felodipine alone and in 3 out of 11 on the placebo day. A statistically significant increase in reported symptoms was found after ramipril alone compared to the combination day. There were no changes in haematology or biochemistry screening tests.

Pharmacokinetics

The concentration time profiles of both ramiprilat and felodipine over the first 24 h are shown in Figure 1. There were no significant alterations of the concentration time profile, AUC(0–96), C_{max} or t_{max} of either drug when the other was coadministered.

Renin–angiotensin–aldosterone system

The time profiles of plasma ACE activity and renin activity over 0–24 h are shown in Figure 2. Ramiprilat produced a significant inhibition of plasma ACE activity which was not altered by the coadministration of felodipine. Plasma ACE inhibition was still 50% at 48 h. No statistically significant differences were found between the different treatment periods for plasma renin activity, although there was a trend for renin activity to be elevated after ramiprilat. No statistically significant differences were found between the four treatment periods for aldosterone.

Noradrenaline

There were no significant differences between the four treatment periods.

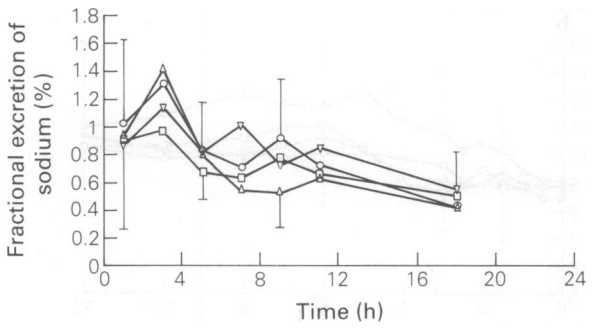

Figure 3 Fractional sodium excretion in urine (%) after ramipril (▽), felodipine ER (△) alone or in combination (○), or placebo (□). Values are mean ± s.d., $n = 11$.

Urinary electrolytes

The fractional excretion of sodium is an index of the proportion of filtered sodium which is not reabsorbed by the tubules, i.e. natriuresis. The time course of the fractional excretion of sodium over 0–24 h is given in Figure 3. Although there were no statistically significant differences in fractional excretion of sodium between the four treatment periods there was a trend for natriuresis to be increased after felodipine during the first 6 h, after which point natriuresis fell to below the placebo rate for the rest of the 24 h period.

Blood pressure and heart rate

There was a highly significant ($P < 0.001$) reduction in systolic blood pressure, both supine and erect, when the combination of ramipril and felodipine was administered (Figure 4). Neither drug exerted a statistically significant effect when administered alone in these healthy normotensive subjects. There was no significant drug–time interaction. The overall reduction in systolic blood pressure by the combination was −8.0 (95% CI +/− 4.4) mm Hg supine and −9.0 (95% CI +/− 4.0) mm Hg erect.

Felodipine alone led to a highly significant ($P < 0.001$) tachycardia in both the supine and erect positions (Figure 4). The supine tachycardia was maximal at 7 h (+10.9 (95% CI +/− 7.8) beats min^{-1}) and was significantly reduced by the addition of ramipril (−8.5 (95% CI +/− 7.8) beats min^{-1}).

The product of systolic blood pressure and heart rate is an index of myocardial oxygen consumption (Gobel *et al.*, 1977; Nelson *et al.*, 1974). Felodipine alone induced a highly significant ($P < 0.001$) increase in rate pressure product (Figure 5). No significant drug–time interaction was observed. The overall elevation of rate pressure product (beats min^{-1} mm Hg) observed with felodipine alone (+791 (95% CI +/− 617) supine and + 1240 (95% CI +/− 802) erect) was abolished by the addition of ramipril (−857 (95% CI +/− 617) supine and −1279 (95% CI +/− 801) erect).

Discussion

This study showed no evidence for a pharmacokinetic interaction between ramipril and felodipine in normal healthy subjects. Felodipine has been reported to cause

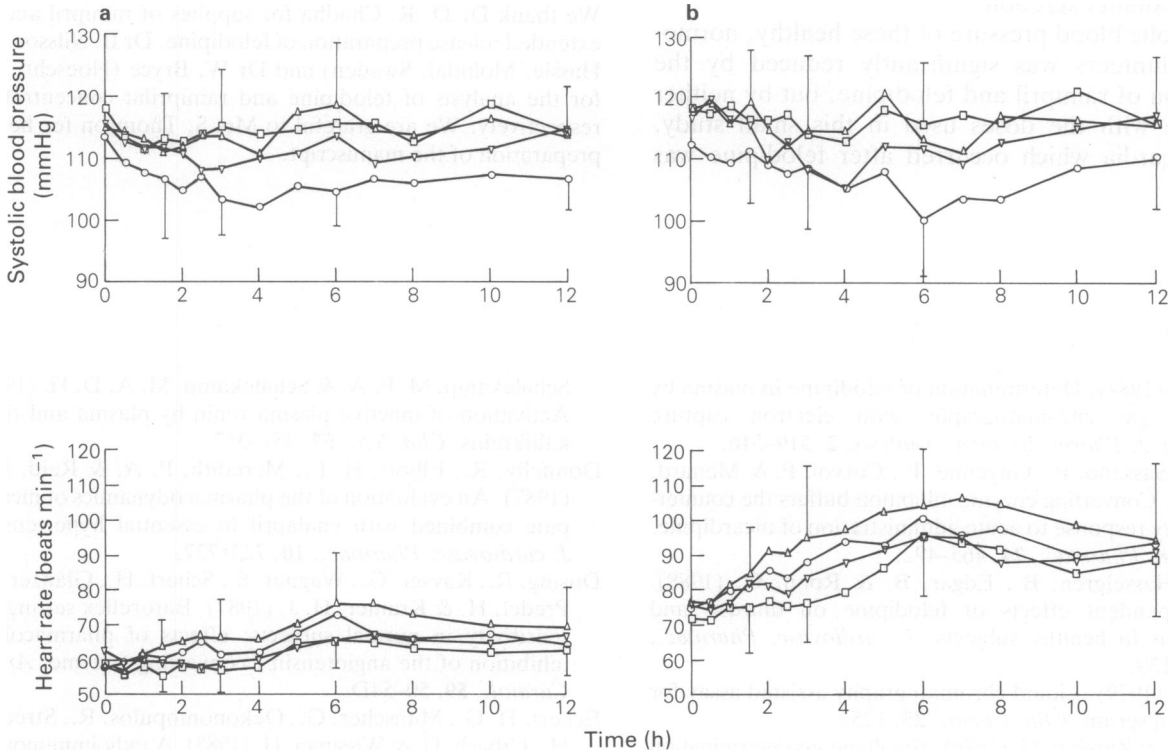

Figure 4 a) Supine and b) erect systolic blood pressure and heart rate responses to ramipril (▽), felodipine ER (△), combination therapy (○) or placebo (□). Values are mean ± s.d., $n = 11$.

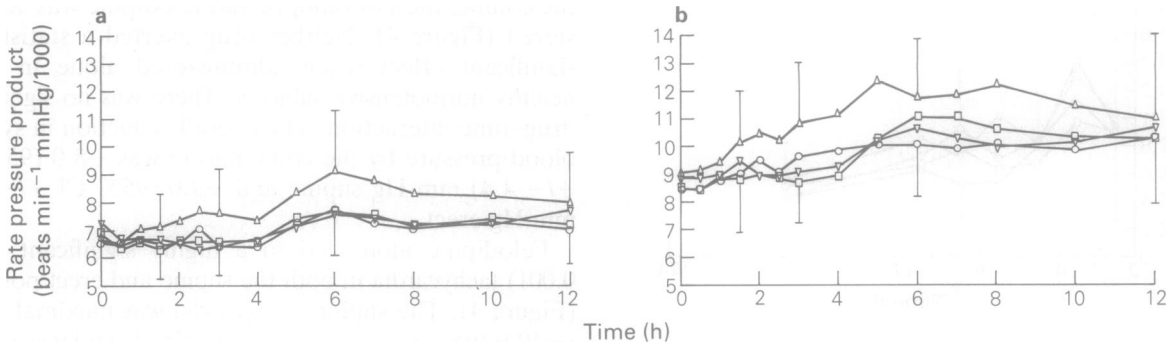

Figure 5 Rate pressure product (RPP) a) supine and b) erect after ramipril (▽) or felodipine (△) alone or in combination (○) compared with placebo (□). Values are mean ± s.d., $n = 11$.

a small increase in the steady state AUC of metoprolol in normal volunteers (Smith *et al.*, 1987), although this interaction was considered unlikely to be of clinical significance.

There was a high incidence of headache reported when felodipine was given alone or added to ramipril in these normal subjects. Thus a 10 mg starting dose of felodipine might be anticipated to be associated with a relatively high incidence of similar complaints in a patient group, particularly when it is known that the AUC in the elderly is about three times greater than in the young for a given dose (Landahl *et al.*, 1988). There was no suggestion that these symptoms attributable to felodipine might be attenuated by the addition of ramipril.

The natriuretic action of felodipine was only observed during the first 6 h, after which point natriuresis fell to below the level of placebo. This pattern of activity is consistent with previous observations in normal volunteers (Bengtsson-Hasselgren *et al.*, 1988), the net effect over a 24 h period being that there is no significant effect on sodium excretion.

The systolic blood pressure of these healthy, normotensive volunteers was significantly reduced by the combination of ramipril and felodipine, but by neither drug alone with the doses used in this small study. The tachycardia which occurred after felodipine was significantly attenuated by the addition of ramipril. The rate pressure product is a clinically useful index which integrates both systolic blood pressure and heart rate. The elevation of rate pressure product observed with felodipine alone was significantly abolished by the addition of ramipril. These results imply that ramipril is able to buffer the reflex heart rate response to the fall in systolic blood pressure induced by the acute administration of felodipine.

The possible mechanisms for this acute pharmacodynamic interaction include enhanced parasympathomimetic activity (Sugimoto *et al.*, 1989), an action on the baroreflex arc (Dusing *et al.*, 1987), or sympathetic inhibition (Bellet *et al.*, 1987). That no significant changes in noradrenaline were seen in the present study does not preclude a postsynaptic site for interference with the interaction of noradrenaline and angiotensin II (Struthers *et al.*, 1987), perhaps at the second messenger level.

We thank Dr D. R. Chadha for supplies of ramipril and the extended release preparation of felodipine. Dr B. Nilsson (AB Hassle, Molndal, Sweden) and Dr W. Bryce (Hoescht, UK) for the analysis of felodipine and ramiprilat concentrations respectively. We are grateful to Mrs S. Thomson for help in preparation of the manuscript.

References

Ahnoff, M. (1984). Determination of felodipine in plasma by capillary gas chromatography with electron capture detection. *J. Pharm. Biomed. Analysis*, **2**, 519–516.

Bellet, M., Sassano, P., Guyenne, P., Corvol, P. & Menard, J. (1987). Converting enzyme inhibition buffers the counter-regulatory response to acute administration of nicardipine. *Br. J. clin. Pharmac.*, **24**, 465–472.

Bengtsson-Hasselgren, B., Edgar, B. & Ronn, O. (1988). Dose-dependent effects of felodipine on diuresis and natriuresis in healthy subjects. *J. cardiovasc. Pharmac.*, **12**, 134–139.

Chiknas, S. (1979). Liquid chromatography assisted assay for A.C.E. in serum. *Clin. Chem.*, **25**, 1259.

da Prada, M. & Zurcher, G. (1976). Simultaneous determination of plasma adrenaline, noradrenaline and dopamine in the femtomole range. *Life Sci.*, **19**, 1161.

Derkx, F. H. M., Tan-Tjiong, H. L., Man in't Veld, A. J., Schalekamp, M. P. A. & Schalekamp, M. A. D. H. (1979). Activation of inactive plasma renin by plasma and tissue kallikreins. *Clin. Sci.*, **57**, 351–357.

Donnelly, R., Elliott, H. L., Meredith, P. A. & Reid, J. L. (1987). An evaluation of the pharmacodynamics of nicardipine combined with enalapril in essential hypertension. *J. cardiovasc. Pharmac.*, **10**, 723–727.

Dusing, R., Kayser, G., Wagner, S., Scherf, H., Glanzer, K., Predel, H. & Kramer, H. J. (1987). Baroreflex setting and sensitivity in normal subjects: effects of pharmacologic inhibition of the angiotensin I converting enzyme. *Am. J. Cardiol.*, **59**, 50–54D.

Eckert, H. G., Munscher, G., Oekonomopulos, R., Strecker, H., Urbach, H. & Wissman, H. (1985). A radioimmunoassay for the angiotensin converting enzyme inhibitor ramipril and its active metabolite. *Arzneimittelforschung*, **35**, 1251–1256.

Edgar, B., Regardh, C. G., Lundborg, P., Romare, S., Nyberg, G. & Ronn, O. (1987). Pharmacokinetic and pharmacodynamic studies of felodipine in healthy subjects after various single, oral and intravenous doses. *Biopharm. Drug. Dispos.*, **8**, 235–248.

Gibaldi, M. & Perrier, D. (1982). In *Pharmacokinetics*, 2nd edition. New York: Marcel Dekker.

Gobel, F. L., Nordstrom, L. A., Nelson, R., Jorgensen, C. R. & Wang, Y. (1977). The rate-pressure product as an index of myocardial oxygen consumption during exercise in patients with angina pectoris. *Circulation*, **57**, 549–556.

Guazzi, M. D., De Cesare, N., Galli, C., Salvioni, A., Tramontana, C., Tamborini, G. & Bartorelli, A. (1984). Calcium-channel blockade with nifedipine and angiotensin converting-enzyme inhibition with captopril in the therapy of patients with severe primary hypertension. *Circulation*, **70**, 279–284.

Heber, M. E., Brigden, G. S., Caruana, M. P., Lahiri, A. & Rafferty, E. B. (1988). First dose response and 24-hour antihypertensive efficacy of the new once-daily angiotensin converting enzyme inhibitor, ramipril. *Am. J. Cardiol.*, **62**, 239–245.

Landahl, S., Edgar, B., Gabrielsson, M., Larsson, M., Lernfelt, B., Lundborg, P. & Regårdh, C. G. (1988). Pharmacokinetics and blood pressure effects of felodipine in elderly hypertensive patients. A comparison with young healthy subjects. *Clin. Pharmacokin.*, **14**, 374–83.

Lees, K. R. & Reid, J. L. (1987). Lisinopril and nifedipine: no acute interaction in normotensives. *Br. J. clin. Pharmac.*, **25**, 307–313.

Liedholm, H. & Melander, A. (1989). A placebo controlled dose-response study of felodipine extended release in hypertensive patients. *J. cardiovasc. Pharmac.*, **14**, 109–113.

McKenzie, J. K. & Clements, J. A. (1974). Simplified radioimmunoassay for serum aldosterone utilising increased antibody specificity. *J. clin. Endocrinol. Metab.*, **38**, 622–627.

Meredith, P. A., Elliott, H. L., McSharry, D. R., Kelman, A. W. & Reid, J. L. (1983). Pharmacokinetics of endralazine in essential hypertension. *Br. J. clin. Pharmac.*, **16**, 27–32.

Meredith, P. A., Elliott, H. L., Pasanisi, F. & Reid, J. L. (1984). Verapamil pharmacokinetics and hepatic and renal blood flow. *Br. J. clin. Pharmac.*, **18**, 272–273.

Nelson, R. R., Gobel, F. L., Jorgensen, C. R., Wang, K., Wang, Y. & Taylor, H. L. (1974). Haemodynamic predictors of myocardial oxygen consumption during static and dynamic exercise. *Circulation*, **50**, 1179–1189.

Pasanisi, F., Meredith, P. A., Elliott, H. L. & Reid, J. L. Verapamil and prazosin: pharmacodynamic and pharmacokinetic interactions. *Br. J. clin. Pharmac.*, **18**, 290P.

Smith, S. R., Wilkins, M. R., Jack, D. B., Kendall, M. J. & Laugher, S. (1987). Pharmacokinetic interactions between felodipine and metoprolol. *Eur. J. clin. Pharmac.*, **31**, 575–578.

Struthers, A. D., Pai, S., Seidlin, P. H., Coutie, J. R. & Morton, J. M. (1987). Evidence in humans for a postsynaptic interaction between noradrenaline and angiotensin II with regard to systolic but not diastolic blood pressure. *J. Hypertension*, **5**, 671–676.

Sugimoto, K., Kumagai, Y., Tateishi, T., Seguchi, H. & Ebihara, A. (1989). Effects on autonomic function of a new angiotensin converting enzyme inhibitor, ramipril. *J. cardiovasc. Pharmac.*, **13**, S40–45.

(Received 6 June 1990, accepted 17 September 1990)