The interactions between nisoldipine and two β -adrenoceptor antagonists—atenolol and propranolol

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- 1 The interactions between the dihydropyridine calcium antagonist nisoldipine and two β -adrenoceptor blocker drugs (atenolol and propranolol) were investigated in two groups of healthy normotensive subjects.
- 2 The steady state plasma concentrations of both β -adrenoceptor blockers were significantly altered by the addition of nisoldipine: for propranolol there were significant increases in $C_{\max}$, by about 50%, and in AUC by about 30% and for atenolol there was a significant increase in $C_{\max}$, by about 20%.
- 3 The addition of nisoldipine was also associated with significant changes in apparent liver blood flow (measured by indocyanine green clearance) from 1.4 to 2.4 l min⁻¹ in the atenolol group and from 1.3 to 2.3 l min⁻¹ in the propranolol group.
- 4 Both nisoldipine- β -adrenoceptor blocker combinations were associated with small enhanced blood pressure reductions e.g. from 104/60 with atenolol alone to 98/50 mm Hg with the combination but there was no alteration to the extent of β -adrenoceptor blockade (as assessed by bicycle ergometry).
- 5 This pharmacodynamic profile in healthy normotensives is consistent with the known therapeutic efficacy of such combination treatments in patients with hypertension and angina.
- 6 It is suggested that there is a pharmacokinetic component to the efficacy of this type of combination, perhaps reflecting vasodilator-induced changes in drug absorption and/or hepatic extraction.

Keywords nisoldipine β -adrenoceptor antagonists interaction

Introduction

The combination of a β -adrenoceptor antagonist with a calcium antagonist drug, typically of the dihydropyridine type, is well established for the treatment of both hypertension and angina. There is evidence in both conditions (Aoki *et al.*, 1978; Dargie *et al.*, 1981; De Caprio *et al.*, 1990; Ekelund & Oro, 1979; Yagil *et al.*, 1983) to suggest that the therapeutic results of such combinations are at least additive but it is not clear whether this only reflects a summation of their pharmacological activities or whether there is also an underlying pharmacokinetic interaction leading to a beneficial alteration in the plasma concentrations of one or other drug. There is evidence that dihydropyridine calcium antagonist drugs, including nisoldipine, as a result of their vasodilator activity, are able to modify splanchnic, hepatic and renal blood flow (Feely, 1984; Meredith *et al.*, 1985) and this affords them

the potential to interfere with the disposition and elimination of concurrently administered drugs.

Within the range of available β -adrenoceptor antagonists there are drugs which differ not only in pharmacological activity (cardioselectivity, partial agonist activity) but also in pharmacokinetic and metabolic aspects. For example, atenolol is not metabolised to any significant extent and is excreted unchanged by the kidney and in the faeces whereas propranolol is subject to extensive first pass hepatic metabolism which might be expected to be particularly susceptible to changes in liver blood flow.

The aim of this study was to examine, in normotensive subjects, the pharmacokinetic and haemodynamic interactions when nisoldipine was added to steady state treatment with either propranolol or atenolol.

Methods

Two groups of eight healthy normotensive males (supine blood pressure less than 140/90 mm Hg, mean age 28 ± 6 years) participated in the study. All subjects were confirmed to have no significant abnormality on clinical examination and routine screening of haematology, biochemistry and ECG, were within 10% of ideal weight for height (71 ± 7 kg), and had taken no medication for at least 2 weeks prior to the study. The study received prior approval from the local Research and Ethics Committee and all subjects gave written informed consent. Subjects were randomly assigned to one of the two treatment groups (atenolol or propranolol) and to one of two treatment schedules and the study was undertaken in a randomised double-blind placebo controlled manner. The atenolol group received background treatment with placebo or atenolol 100 mg daily and the propranolol group received placebo or propranolol 160 mg daily. The study, which was designed specifically to evaluate the effects of adding the calcium antagonist, involved two phases of drug treatment, each of 2 weeks duration, and during the second week of each phase additional treatment was administered, either nisoldipine 20 mg once daily or matched placebo capsules (Figure 1). This design allowed the following treatment combinations to be evaluated when the subjects attended for a series of 4 study days at weekly intervals:

- 1) β -adrenoceptor blocker (steady state) plus first dose nisoldipine
- 2) β -adrenoceptor blocker (steady state) plus steady state nisoldipine
- 3) Placebo plus placebo
- 4) β -adrenoceptor blocker (steady state) plus placebo.

On each study day subjects reported to the Clinical Pharmacology Research Unit having fasted from 22.00 h on the preceding night and having avoided alcohol, tobacco and caffeine-containing beverages from the same time. Baseline haemodynamic measurements were made at least 20 min supine rest following the insertion of a cannula into an antecubital vein.

Pharmacodynamics

Blood pressure and heart rate, erect and supine, were measured using a semiautomated sphygmomanometer (Sentron, Bard Medical) at baseline (time 0 and after 0.5, 1, 1.5, 2, 3, 4, 6 and 8 h). The extent of β -adrenoceptor antagonism was further assessed on each study day by the heart rate response to submaximal exercise (75% of a predetermined maximum) for 5 min

on a bicycle ergometer at two times: 2.5 h (early) and 5 h after dosing (late). Hepatic blood flow was assessed 1 h after drug administration following the separate intravenous injection of indocyanine green and by subsequent measurement of its clearance (assuming complete hepatic extraction) from venous blood samples obtained at 3 min intervals for 21 min (Meredith *et al.*, 1985). Effective renal plasma flow (ERPF) and glomerular filtration rate (GFR) were also determined 1 h after drug administration from the clearance of radio pharmaceuticals, as previously described (Meredith *et al.*, 1985).

Pharmacokinetics

Venous plasma for drug assays was collected at 0, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8 and 24 h after dosing for the subsequent measurement of atenolol by h.p.l.c. assay (Yee *et al.*, 1979), for propranolol by h.p.l.c. assay (Girault & Fourtillan, 1981) and for nisoldipine by g.c. with electron capture (Ahr, personal communication). Each assay was specific with no cross-reactivity between drugs. For atenolol, the interassay precision was 8.1%, the intra-assay precision was 5.2% and the sensitivity was 10 ng ml^{-1} . The corresponding figures for propranolol were 6.8%, 4.3% and 20 ng ml^{-1} and for nisoldipine 9.3%, 5.9% and 0.02 ng ml^{-1} .

The pharmacokinetic profiles of both atenolol and propranolol were most appropriately described by a one-compartment open model with first order absorption and for nisoldipine by a one-compartment model with zero order absorption. Parameter estimates were obtained by nonlinear least squares fitting using an 'in house' programme based on the Marquardt algorithm (Bevington, 1969) with equal weighting for all data.

Statistical analysis of blood pressure, heart rate, ICG clearance, GFR and ERPF, chronotropic responses to exercise and pharmacokinetic parameters was by repeated measures analysis of variance. For individual time points statistical significance was further assessed by application of the Scheffe test. Results throughout are expressed as mean $\pm$ s.d.

Results

Blood pressure and heart rate

The measurements of blood pressure and heart rate are summarised in Table 1 and illustrated for supine diastolic pressure in Figures 2a and 2b. Overall the results for both the atenolol and propranolol groups were similar, with the active treatments producing significant differences from placebo but with little discrimination between the different active treatments. For example, erect blood pressure (expressed as an average of all readings obtained during the 8 h study period) was 114/68 mm Hg with atenolol. The addition of nisoldipine gave further small reductions, which were not statistically significant, to 101/57 mm Hg with the first dose and to 100/59 mm Hg with continued dosing. Only for supine diastolic blood pressure in the atenolol group did the additional effect of nisoldipine achieve statistical significance with both first dose and continued nisoldipine

Subjects were randomly allocated to atenolol or propranolol and to schedule A or B.

Figure 1 Study design.

Table 1 Summary of blood pressure and heart rate results (expressed as the averages from all readings in each individual during the 8 h study days)

	Placebo	β -adrenoceptor blocker alone	β -adrenoceptor blocker plus nisoldipine 1st dose	1 week
<i>Atenolol group</i>				
<i>Supine</i>				
Blood pressure (mm Hg)	114/61	104*/60	100*/52**	98*/50**
Heart rate (beats min ⁻¹)	58	50*	55*	52*
<i>Erect</i>				
Blood pressure (mm Hg)	114/68	105*/60*	101*/57*	100*/59*
Heart rate (beats min ⁻¹)	79	64*	69*	66*
<i>Propranolol group</i>				
<i>Supine</i>				
Blood pressure (mm Hg)	113/62	106*/57*	106*/53*	103*/53*
Heart rate (beats min ⁻¹)	63	54*	55*	55*
<i>Erect</i>				
Blood pressure (mm Hg)	114/70	104*/63*	103*/60*	103*/58*
Heart rate (beats min ⁻¹)	84	68*	70*	72*

* $P < 0.05$ vs placebo, ** $P < 0.05$ vs β -adrenoceptor blocker alone.

Figure 2 Supine diastolic blood pressure, a) following placebo ($\circ$), atenolol alone (Δ), atenolol plus first dose nisoldipine ($\square$) and atenolol plus steady state nisoldipine ($\blacksquare$); b) following placebo ($\circ$), propranolol alone (∇), propranolol plus first dose nisoldipine ($\square$) and propranolol plus steady state nisoldipine ($\blacksquare$).

causing reductions in blood pressure which were significantly greater than with the β -adrenoceptor blocker alone (Figure 2b).

Chronotropic responses to submaximal exercise

These data are illustrated for propranolol in Figure 3. Both atenolol and propranolol were associated with significant reductions in the resting (pre-exercise) heart

Figure 3 Chronotropic responses to exercise at both early (left panel) and late times (right panel) for the propranolol group following placebo ($\circ$), propranolol alone (∇), propranolol plus first dose and steady state nisoldipine ($\square$, $\blacksquare$).

Table 2 Indices of liver and kidney function

	Placebo	Atenolol alone	Atenolol plus nisoldipine 1st dose	Atenolol plus nisoldipine 1 week	Placebo	Propranolol alone	Propranolol plus nisoldipine 1st dose	Propranolol plus nisoldipine 1 week
Apparent liver blood flow (l min ⁻¹)	1.66 ± 0.44	1.42 ± 0.42	2.38 ± 0.71*	2.16 ± 0.42*	1.58 ± 0.47	1.33 ± 0.36*	2.27 ± 0.67**	2.36 ± 0.80**
Glomerular filtration rate (ml min ⁻¹)	115 ± 14	112 ± 9	115 ± 14	110 ± 13	111 ± 25	101 ± 23	104 ± 22	115 ± 24
Effective renal plasma flow (ml min ⁻¹)	579 ± 97	546 ± 82	637 ± 114	573 ± 43	532 ± 117	503 ± 88	534 ± 120	572 ± 129

* $P < 0.05$ vs placebo, ** $P < 0.01$ vs placebo.

rate, the maximum heart rate responses to exercise, and the increment in heart rate. Neither first dose nor continued treatment with nisoldipine significantly interfered with these heart rate reductions.

Apparent liver blood flow

The addition of the first dose of nisoldipine to steady state atenolol treatment caused a significant increase in liver blood flow to 2.4 l min⁻¹, compared with 1.4 l min⁻¹ with atenolol alone, and this was sustained at 2.2 l min⁻¹ with steady state treatment (Table 2).

The results with propranolol followed a similar pattern although with propranolol alone there was a small but significant reduction in liver blood flow to 1.3 l min⁻¹ compared to 1.6 l min⁻¹ with placebo. The addition of the first dose of nisoldipine was associated with a significant increase to 2.3 l min⁻¹ and this was sustained at 2.4 l min⁻¹ with steady state nisoldipine treatment.

The volume of distribution of indocyanine green was not significantly altered by any drug treatment.

Renal function

These results are also summarised in Table 2. There were no significant differences attributable to any treatment for glomerular filtration rate (GFR) or effective renal plasma flow (ERPF). There was a rank order effect for the mean ERPF to be lowest with the β -adrenoceptor blocker, 503 ml min⁻¹ with propranolol, and for the highest value to occur after acute nisoldipine, 637 ml min⁻¹ in the atenolol group. The results for GFR were closely similar in both groups, for all treatments, although the lowest value, 101 ml min⁻¹, was obtained with propranolol alone.

Pharmacokinetics

The plasma concentration-time profiles for each β -adrenoceptor blocker are illustrated in Figures 4a and 4b and the derived pharmacokinetic parameters are summarised in Tables 3 and 4.

Atenolol There were significant increases in peak atenolol concentrations (C_{max}) with both acute and chronic nisoldipine: Mean C_{max} was 455 ng ml⁻¹ with atenolol alone, 540 ng ml⁻¹ with acute nisoldipine and

Figure 4 Plasma drug concentration-time profiles a) atenolol group (Δ atenolol, $\square$ acute nisoldipine, $\blacksquare$ chronic nisoldipine); b) propranolol group (∇ propranolol, $\square$ acute nisoldipine, $\blacksquare$ chronic nisoldipine).

547 ng ml⁻¹ with steady state nisoldipine. There was a slight increase in AUC for atenolol when combined with nisoldipine but this did not achieve significance. The elimination half-life ($t_{1/2}$) and time to peak concentration (t_{max}) for atenolol were not significantly affected by combination with nisoldipine.

Propranolol The AUC for propranolol was significantly increased with the nisoldipine combinations: 1556 for propranolol alone compared with 2098 following first dose nisoldipine and 2482 ng ml⁻¹ h for steady state

Table 3 Pharmacokinetic parameters of atenolol and propranolol

	Atenolol	Atenolol plus nisoldipine		Propranolol	Propranolol plus nisoldipine	
		1st dose	1 week		1st dose	1 week
$C_{\max}$ (ng ml ⁻¹)	455 ± 135	540 ± 159*	547 ± 146*	143 ± 44	222 ± 67†	221 ± 66*
$t_{\max}$ (h)	2.9 ± 1.1	2.7 ± 1.0	2.6 ± 1.0	2.8 ± 1.5	2.2 ± 1.4	2.2 ± 1.0
AUC (ng ml ⁻¹ h)	5854 ± 2291	6987 ± 2130	6844 ± 2269	1556 ± 1135	2098 ± 1501†	2482 ± 2099†
$t_{1/2,z}$ (h)	7.8 ± 1.9	7.4 ± 2.4	6.6 ± 1.7	5.4 ± 2.6	5.2 ± 2.3	6.1 ± 3.6

* $P < 0.05$ vs atenolol, † $P < 0.05$ vs propranolol.

Table 4 Pharmacokinetic parameters of nisoldipine (mean ± s.d.)

	Propranolol group		Atenolol group	
	Acute	Steady state	Acute	Steady state
AUC (ng ml ⁻¹ h)	27.3 ± 8.2	27.9 ± 9.4	24.8 ± 5.7	26.4 ± 7.2
(Change)		(+0.6 ± 1.9)		(+1.6 ± 8.8)
$t_{1/2,z}$ (h)	5.9 ± 1.3	6.7 ± 1.0	6.2 ± 1.3	6.1 ± 1.2
(Change)		(+0.8 ± 0.7)*		(-0.1 ± 0.5)
$C_{\max}$ (ng ml ⁻¹)	2.9 ± 1.2	2.5 ± 1.1	2.3 ± 0.6	2.5 ± 0.8
(Change)		(-0.4 ± 0.3*)		(+0.2 ± 1.0)
$t_{\max}$ (ng ml ⁻¹)	1.9 ± 0.5	2.0 ± 0.5	1.9 ± 0.4	2.0 ± 0.6
(Change)		(+0.1 ± 0.3)		(+0.1 ± 0.5)

* $P < 0.02$.

nisoldipine. A similar pattern was observed for the $C_{\max}$ values which were significantly increased by the nisoldipine combinations. No significant differences were observed in elimination half-life or in time to peak concentration.

Nisoldipine The pharmacokinetic parameters for nisoldipine in combination with steady state β -adrenoceptor blocker treatment are given in Table 4. (This study did not investigate the pharmacokinetics of nisoldipine alone).

With atenolol no significant changes were observed in any of the kinetic parameters for nisoldipine. In contrast, with propranolol there was a small but significant prolongation in half-life from 5.9 h on acute dosing to 6.7 h at steady state and there was a similar small but significant decrease in $C_{\max}$ in translation from acute to steady state nisoldipine. No significant changes in AUC were observed in translation from acute to steady state nisoldipine with either atenolol or propranolol.

Subjective assessment

There were volunteered complaints of tiredness (six subjects), particularly during the exercise testing (but not specifically identifiable with any individual treatment): headache (six subjects) (particularly with first dose nisoldipine, $n = 5$); and other orthostatic symptoms (eight subjects), again particularly with the first dose of nisoldipine, ($n = 4$). Overall, these side effects were not considered unduly troublesome by any subject and generally the drug treatments were well tolerated. No significant abnormalities were detected on the routine haematological or biochemical screenings.

Discussion

The administration of a β_1 -selective (atenolol) and a non-selective (propranolol) β -adrenoceptor antagonist resulted in small but significant falls in blood pressure and heart rate, both supine and erect. In general, the addition of the calcium antagonist nisoldipine resulted in further small falls in blood pressure without any significant further change in heart rate. From the exercise tests there was no evidence to suggest that the extent of β -adrenoceptor blockade was significantly compromised by the addition of nisoldipine. These results, in healthy normotensives, are consistent with the known advantageous therapeutic effects of such combinations in both hypertension and angina.

The principal pharmacokinetic findings were that nisoldipine, after single and multiple doses, significantly increased the peak plasma concentrations of both β -adrenoceptor blockers and, in addition, significantly increased the AUC of propranolol. The elimination half-life of neither β -adrenoceptor blocker was affected by nisoldipine. With respect to nisoldipine, the design of this study examined only the influence of β -adrenoceptor treatment on the kinetics of nisoldipine during its transition from acute to steady state treatment. Although propranolol produced statistically significant changes in the half-life and peak concentrations of nisoldipine, the changes were small and, overall, there was no evidence that either β -adrenoceptor blocker had substantially influenced the pharmacokinetics of nisoldipine.

Pharmacokinetic interactions between β -adrenoceptor blockers and dihydropyridine calcium antagonist have been the subject of several previous reports but the results, to date, have been inconsistent. For example, a

single dose study with propranolol and nisoldipine has reported results which are closely comparable with the findings of this present study insofar as nisoldipine increased the $C_{\max}$ and AUC of propranolol by 68 and 43%, respectively, and there were also significant corresponding increases in the $C_{\max}$ and AUC of nisoldipine (Levine *et al.*, 1988). An important additional aspect of that study was evidence of enhanced β -adrenoceptor blockade. Similarly, nifedipine has been shown to increase the $C_{\max}$ and AUC of propranolol (Schoors *et al.*, 1990). In contrast, other single dose studies have reported no evidence of a significant kinetic interaction between nifedipine and atenolol (Rosenkranz *et al.*, 1986) or between nifedipine and atenolol (Vercruysse *et al.*, 1990). However, it is apparent in the first of those studies that the combination treatment was associated with consistently higher plasma concentrations of atenolol at all early time points and that the average $C_{\max}$ was about 15% greater. The second study similarly shows marginally higher plasma concentrations with the combination. None of these differences is statistically significant. Other studies with multiple doses of nifedipine have shown a significant effect on the disposition of propranolol (but not betaxolol) (Vinceneux *et al.*, 1986) or alternatively no significant effects on the disposition of atenolol, propranolol and metoprolol (Gangji *et al.*, 1984; Kendall *et al.*, 1984), although two of these latter studies again showed higher values for the $C_{\max}$ of the β -adrenoceptor blocker. With felodipine a significant kinetic interaction has been identified with metoprolol (Kendall *et al.*, 1984). Thus, although not all studies have shown statistical significance, the weight of evidence suggests that there is

a significant interaction between dihydropyridine calcium antagonists and β -adrenoceptor blockers (particularly, those which undergo hepatic metabolism) and it appears likely that the underlying mechanisms relate to changes in the extent of vasodilatation of the splanchnic, portal and hepatic circulations. In this study, the indices of hepatic blood flow and of renal plasma flow tended to be reduced by β -adrenoceptor blocker treatment, particularly with propranolol, and increased when nisoldipine was added. Since the $C_{\max}$, and to some extent the $t_{\max}$, for both a hydrophilic (atenolol) and a lipophilic (propranolol) β -adrenoceptor blocker were affected it suggests that the absorptive process is being influenced by the calcium antagonist. With propranolol, which undergoes extensive presystemic metabolism, it is likely that there additionally is an effect on first-pass hepatic extraction to account for the significant increase in AUC without any detectable change in terminal half-life.

In summary, this study presents evidence of pharmacokinetic interactions with both acute and multiple doses of nisoldipine when both propranolol and atenolol were at steady state. These kinetic changes were most marked with propranolol, presumably as a result of its greater dependency upon hepatic extraction, and it therefore appears likely that the beneficial therapeutic effects of the combination of β -adrenoceptor blockers with calcium antagonists reflects, in part, additional pharmacological activity resulting from altered drug absorption or disposition.

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References

- Aoki, K., Kondo, S., Mochizuki, A., Yoshida, T., Kato, S., Kato, K. & Takikawa, K. (1978). Antihypertensive effect of cardiovascular Ca^{2+} -antagonist in hypertensive patients in the absence and presence of beta-adrenergic blockade. *Am. Heart J.*, **96**, 218–226.
- Bevington, P. R. (1969). *Data reduction and error analysis for the physical sciences*, pp. 235–236. New York: McGraw-Hill.
- Dargie, H. J., Lynch, P. G., Krikler, D. M., Harris, L. & Krikler, S. (1981). Nifedipine and propranolol, a beneficial drug interaction. *Am. J. Med.*, **71**, 676–682.
- De Caprio, L., Papa, M., Acanfora, D., Abete, P., Gallucci, F., Covelluzzi, F., Cicatiello, A. M. & Rengo, F. (1990). Acute effects of nisoldipine, propranolol and their combination in patients with chronic stable angina, a double-blind, randomised, cross-over, placebo-controlled study. *J. cardiovasc. Pharmacol.*, **16**, 325–330.
- Ekelund, L. G. & Oro, L. (1979). Antianginal efficiency of nifedipine with and without a beta-blocker, studied with exercise test. A double-blind, randomised, subacute study. *Clin. Cardiol.*, **2**, 203–211.
- Feely, J. (1984). Nifedipine increases and glyceryl trinitrate decreases apparent liver blood flow in normal subjects. *Br. J. clin. Pharmacol.*, **17**, 83–85.
- Gangji, D., Jubent, M., Niset, G., Wathieu, M., Degreve, M., Bellens, R., Poortmans, J., Degre, S., Fitzsimmons, T. J. & Herchuelz, A. (1984). Study of the influence of nifedipine on the pharmacokinetics and pharmacodynamics of propranolol, metoprolol and atenolol. *Br. J. clin. Pharmacol.*, **17**, 29S–35S.
- Girault, J. & Fourtillan, J. (1981). Beta blocking agents, determination of biological levels using HPLC. *J. liquid Chromatogr.*, **4**, 483–500.
- Kendall, M. J., Jack, D. B., Laughner, S. J., Lobo, J. & Rolf Smith, S. (1984). Lack of a pharmacokinetic interaction between nifedipine and the β -adrenoceptor blockers metoprolol and atenolol. *Br. J. clin. Pharmacol.*, **18**, 331–335.
- Levine, M. A. H., Ogilvie, R. I. & Leenen, F. H. H. (1988). Pharmacokinetic and pharmacodynamic interactions between nisoldipine and propranolol. *Clin. Pharmacol. Ther.*, **43**, 39–48.
- Meredith, P. A., Pasanisi, F., Elliott, H. L. & Reid, J. L. (1985). The effect of nisoldipine on apparent liver blood flow and effective renal plasma flow. *Br. J. clin. Pharmacol.*, **20**, 235–237.
- Rosenkranz, B., Ledermann, H. & Frolich, J. C. (1986). Interaction between nifedipine and atenolol, pharmacokinetics and pharmacodynamics in normotensive volunteers. *J. cardiovasc. Pharmacol.*, **8**, 943–949.
- Schoors, D. F., Vercruysse, I., Musch, G., Massart, D. L. & Dupont, A. G. (1990). Influence of nifedipine on the pharmacokinetics and pharmacodynamics of propranolol in healthy volunteers. *Br. J. clin. Pharmacol.*, **29**, 497–501.
- Smith, S. R., Wilkins, M. R., Jack, D. B., Kendall, M. J. & Laughner, S. (1987). Pharmacokinetic interactions between

- felodipine and metoprolol. *Eur. J. clin. Pharmac.*, **31**, 575–578.
- Vercruysse, I., Schoors, D. F., Musch, G., Massart, D. L. & Dupont, A. G. (1990). Nicardipine does not influence the pharmacokinetics and pharmacodynamics of atenolol. *Br. J. clin. Pharmac.*, **30**, 499–500.
- Vinceneux, P. H., Canal, M., Domart, Y., Roux, A., Cascio, B., Orofiamma, B., Larribaud, J., Flouvat, B. & Carbon, C. (1986). Pharmacokinetic and pharmacodynamic interactions between nifedipine and propranolol or betaxolol. *Int. J. clin. Pharmac. Ther. Toxicol.*, **24** 153–158.
- Yagil, Y., Leibel, B., Kobrin, I., Stessman, J. & Ishay, D. B. (1983). The combination of propranolol and nifedipine in the treatment of hypertension, acute and long-term effects. *Postgrad. med. J.*, **59** (Suppl. 2), 114–115.
- Yee, Y. G., Rubin, P. & Blaschke, T. (1979). Atenolol determination of HPLC and fluorescence detection. *J. Chromatogr.*, **171**, 357–362.

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