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Pharmacokinetics and disposition of nifedipine and acebutolol as a fixed combination or given separately after single and repeated dose in healthy subjects

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Acebutolol, a β-blocking drug, has been shown to be clinically effective in hypertension, angina pectoris and certain cardiac arrhythmias. Its kinetics as well as those of its main active metabolite, diacetolol, have been described under different conditions (Meffin et al., 1976; Flouvat et al., 1981). Nifedipine, a dihydropyridine (Braunwald, 1982), is clinically effective in hypertension and angina pectoris. Several formulations were developed and the kinetics thereof reported (Foster et al., 1983; Raemsch and Sommer, 1983).

It has often been observed that a combination of acebutolol and nifedipine in the treatment of angina pectoris or hypertension is more effective to that of a monotherapy with either drug (De Ponti et al. 1981).

A fixed combination of acebutolol and nifedipine is considered an improvement in the treatment of hypertension in that it was possible to reduce the doses of these drugs and improve compliance (Lejeune et al., 1985). Soluble nifedipine in soft gelatin capsule has a rapid in vivo release whereas milled nifedipine in tablet form has a slow in vivo release (Raemsch and Sommer, 1983). This new tablet, BAY 1 5240, contains 10 mg nifedipine, microfine crystals, and 100 mg acebutolol. The aim of this double-blind triple crossover study was to compare the pharmacokinetic parameters and disposition of the two components after a single or repeated dose of the fixed combination, of nifedipine microfine crystals and of acebutolol in 12 normotensive healthy adult volunteers, 6 males and 6 females, each volunteer being its own control.

The study was carried out in the clinic, in quiet rooms and under permanent medical supervision. One female volunteer did not attend and was not replaced. Each treatment lasted 5 days in order to reach steady-state kinetics. Each treatment period was separated by a 9-day wash-out period. All tablets were taken at 08.00 h after overnight fasting with 500 ml of water to achieve a urine output during a 55 min period after treatment. Blood

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samples (10 ml) were taken from an antecubital vein and collected in EDTA-tubes 15 min before as well as 15, 30 and 60 min, and 2, 3, 4, 6, 8, 10, 12 and 24 h on the first and the fifth day of each treatment period for the determination of acebutolol, diacetolol and nifedipine plasma levels. The urine collection times were chosen to obtain at least two blood level determinations in each period and not to interfere with blood collection and other measurements.

Urinary excretion of nifedipine metabolites was determined on the 5th day of the nifedipine and the fixed combination periods, by pooling urine over 72 h period beginning at drug intake. Urinary excretion of acebutolol and diacetolol was measured on the 1st and 5th day of the acebutolol and the fixed combination periods in the different urine collections.

The discrepancy observed between the plasma profile of nifedipine alone or combined with acebutolol, prompted us to study the kinetics of a single 20 mg dose of nifedipine, microfine crystals, as a 360 mg coated tablet in the same volunteers, 3 months later (Period D). This tablet has already been studied in hypertension and angina pectoris. The complementary study was conducted to clarify the question of whether the pharmacokinetic data of nifedipine correlate with the in vitro release data of nifedipine of different weight.

Acebutolol and diacetolol were determined by HPLC according to Flouvat et al. (1981) using a 3 μm C18 column (Excalibar-Applied Sciences). Nifedipine plasma levels were measured according to Lesko et al. (1983) and nifedipine urinary metabolites according to Raemsch and Sommer (1983). The results were analyzed using the paired *t*-test.

No difference could be found between the acebutolol/diacetolol kinetics of the first and the fifth day of both fixed combinations and acebutolol treatments (Table 1). Significant differences consisting of a lower C_{max} ($P < 0.05$), a delayed T_{max} ($P < 0.05$) and a prolonged $t_{1/2}$ ($P < 0.05$) after 10 mg nifedipine (B) than after the fixed combination (A), both on day 1 and day 5 were observed. In contrast, the area under the curves (AUCs) of nifedipine after the fixed combination did not differ from those found after 10 mg nifedipine (Fig. 1 and Table 1). The AUC for nifedipine on day 1 and day 5 of the fixed combination (A) and the C_{max} for nifedipine on day 1 and day 5 of nifedipine (B) were significantly

TABLE 1

KINETICS DATA

	C_{max} (μg/l)	T_{max} (h)	$T_{1/2}$ (h)	AUC_0^∞ (μg · h/l)
day 1 (n = 11)				
(A) acebutolol	156.3 ± 20.4	2.1 ± 0.2	2.58 ± 0.23	974.2 ± 93.3
diacetolol	134.2 ± 26.5	3.5 ± 0.5	4.83 ± 0.69	1608.5 ± 263.3
nifedipine	61.5 ± 7.0	0.9 ± 0.1	2.70 ± 0.43	234.8 ± 24.3
(B) nifedipine 10 mg	27.4 ± 2.1	1.4 ± 0.2	4.53 ± 0.54	193.0 ± 19.7
(C) acebutolol	131.5 ± 28.3	2.3 ± 0.2	2.86 ± 0.39	814.3 ± 131.8
diacetolol	113.9 ± 26.1	2.9 ± 0.2	5.41 ± 0.60	1097.2 ± 209.0
(D) nifedipine 20 mg	91.2 ± 11.1	1.9 ± 0.3	4.06 ± 0.52	458.8 ± 38.4
day 5 (n = 11)				
(A) acebutolol	159.1 ± 27.7	1.9 ± 0.1	3.38 ± 0.69	994.1 ± 139.3
diacetolol	127.8 ± 25.3	2.2 ± 0.1	7.47 ± 1.20	1.535.5 ± 234.5
nifedipine	62.6 ± 4.9	0.8 ± 0.1	2.82 ± 0.30	191.4 ± 26.1
(B) nifedipine 10 mg	37.0 ± 5.1	1.5 ± 0.2	5.54 ± 0.82	218.3 ± 27.2
(C) acebutolol	153.6 ± 18.5	2.6 ± 0.4	3.48 ± 0.74	1059.5 ± 113.7
diacetolol	114.2 ± 17.6	3.0 ± 0.4	7.57 ± 1.13	1456.4 ± 289.7

($P < 0.05$) different (Table 1).

The kinetics after 20 mg nifedipine (D) investigated as a complementary study were characterized by a higher C_{max} ($P < 0.05$) and delayed T_{max} ($P < 0.05$) than those of the fixed combination and the 10 mg nifedipine tablets (Table 1).

In vitro, about 80% of nifedipine was released after 1 h from the fixed combination, and after 2 h from 20 mg nifedipine tablets. In contrast, only 73% of nifedipine was released after 6 h from 10 mg nifedipine tablets. As far as urinary recoveries of acebutolol, diacetolol and nifedipine metabolites are concerned, no statistically significant differences were observed between the three formulations.

The relative bioavailability of nifedipine was the same after the fixed combination and the 10 mg nifedipine tablet as assessed by the AUCs and the urinary excretion of nifedipine metabolites. The nifedipine plasma profile after the fixed combination is more similar to that of nifedipine capsules than that of nifedipine tablets (Raemsch and Sommer, 1983). The in vitro release of nifedipine from the 80 mg tablet or from the 360 mg fixed combination confirm the in vivo data mainly concerning the rate of dissolution. Under these conditions, comparisons using other parameters than AUCs and urinary recoveries are not meaningful and a complementary study was justified. The influence of the total weight of the tablet was first studied with the 20 mg microfine nifedipine tablet (total weight 360 mg) already used in hypertension and angina pectoris clinical trials. The results of this complementary study confirm those obtained after the 10 mg microfine nifedipine tablet (same T_{max} and relative C_{max}) in the same volunteers. Consequently the more rapid release of nifedipine from the fixed combination tablet could be promoted by the presence of a hydrosoluble salt, in this case acebutolol hydrochloride.

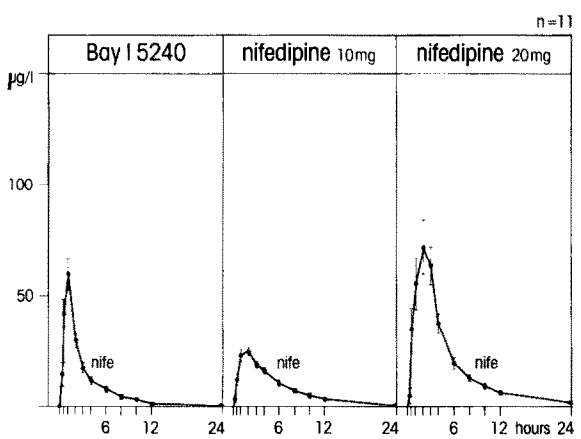

Fig. 1. Nifedipine plasma levels after day 1.

As recently reported, two selective β-blockers (metoprolol, atenolol) studied in free combination with nifedipine did not affect the pharmacokinetics of either drug (Kendall et al., 1984). These findings are in agreement with another report in which the propranolol T_{max} only was influenced but not the pharmacokinetics of atenolol and metoprolol, nor other pharmacokinetic parameters of propranolol (Gangji et al., 1984).

The pharmacokinetics of acebutolol (plasma levels, urine recovery) and its main active metabolite, diacetolol, in the fixed combination tablet of acebutolol with microfine nifedipine and two 50 mg acebutolol tablets are similar.

In conclusion, this new formulation containing nifedipine as microfine crystals and acebutolol in a fixed combination tablet is characterized by a more rapid release of nifedipine without influencing the disposition of acebutolol in healthy normotensive volunteers. We speculate that this more rapid release of nifedipine from the combination tablet could be promoted by the presence of a hydrosoluble salt, acebutolol hydrochloride.

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