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Influence of nicardipine on the pharmacokinetics and pharmacodynamics of propranolol in healthy volunteers

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1 The influence of a single oral dose of nicardipine 30 mg on the pharmacokinetics and pharmacodynamics of propranolol 80 mg was investigated in twelve healthy volunteers.
2 Co-administration of nicardipine significantly increased the AUC and the mean C_{max} of propranolol.
3 Blood pressure and heart rate tended to decrease more when propranolol and nicardipine were administered together than when propranolol was given alone, but differences are of doubtful significance.
4 The results indicate that nicardipine alters the pharmacokinetics of propranolol by impaired hepatic 'first-pass' clearance, but pharmacodynamics were little affected.

Keywords nicardipine pharmacodynamics pharmacokinetics propranolol

Introduction

Combination therapy with calcium-entry blockers, such as dihydropyridines and β-adrenoceptor blockers, is increasingly used in the management of ischaemic heart disease and hypertension, as it is considered to be more effective than monotherapy with either drug (Hanet *et al.*, 1988; Harris *et al.*, 1982; Lessum *et al.*, 1989; Lynch *et al.*, 1980; Packer, 1989; Pouleur *et al.*, 1984). Calcium-entry blockers, such as nifedipine, have been reported to either increase, decrease, or have no effect on plasma levels of propranolol (Butleir *et al.*, 1984; Gangji *et al.*, 1984; Kleinbloesem *et al.*, 1985). The difficulties the different investigators had in demonstrating significant differences, are due to the small number of subjects in the different studies and the large individual variability of drug levels. Apparently, the route of administration can also be a factor in the occurrence in pharmacokinetic interactions, mainly for drugs subject to extensive first-pass effect (Cruickshank & Prichard, 1988).

Combination of propranolol and nifedipine increases the plasma levels of nifedipine, compared with those obtained with nifedipine alone (Zylber-Katz *et al.*, 1988). Propranolol is almost completely absorbed from the gastrointestinal tract and largely metabolized in the liver. Due to an extensive first-pass hepatic clearance, the systemic bioavailability after oral intake is only about 30–40% and highly variable drug concentrations are seen (Cruickshank & Prichard, 1988). Calcium-entry blockers, such as nicardipine, a recently developed dihydropyridine derivative, decrease vascular smooth muscle tone, thereby reducing vascular resistance and increasing blood flow. These effects have been reported in the mesenteric and hepatic vascular beds (Sorkin & Clissold, 1987). The possibility that nicardipine might influence the pharmacokinetics and the haemodynamics of propranolol by e.g. its effect on the splanchnic blood flow and hence change systemic bioavailability of propranolol, prompted us to study the influence of nicardipine on the pharmacokinetics and pharmacodynamics of propranolol.

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Methods

Subjects

Six healthy male volunteers (23–29 years, mean weight 77 kg) and six healthy female volunteers (22–41 years, mean weight 62 kg) participated in the study. They were not on any medication and were requested to abstain from smoking and alcohol during the study. The study was conducted in accordance with the provisions of the Declaration of Helsinki. Verbal informed consent was obtained from each participant and the study protocol was approved by the local hospital ethics committee.

Study protocol

The subjects were investigated on two separate occasions, at 1 week intervals and after an overnight fast. At 08.00 h they attended the metabolic unit and a heparin lock was placed in a forearm vein for blood sampling. The subjects were randomly allocated to receive either propranolol (80 mg, orally) alone or propranolol (80 mg) together with nicardipine (30 mg, orally) at 09.00 h. Blood pressure was taken before and 2, 4 and 8 h after drug ingestion, utilizing a standard mercury sphygmomanometer (phase V Korotkoff sound for diastolic pressure). Blood pressure was defined as the mean of three readings taken in the seated position after 15 min of rest. Heart rate was measured by counting pulsations at the radial artery during 1 min.

Blood samples, for determination of the plasma levels of propranolol, were obtained prior to the morning dose and 20, 40, 60, 90, 120, 180, 240, 360, 480 and 540 min following administration of the dose. Each time 10 ml of blood was collected in a heparinized sterile syringe (Sarstedt®). Blood samples were immediately centrifuged for 30 min at 3000 *g* and the plasma was separated and stored at −20° C until analysed.

Analytical procedure

The assay of propranolol in plasma was performed using h.p.l.c. as analytical technique in combination, with solid phase extraction for the sample treatment, according to a method previously published by Musch & Massart (1988). The coefficient of variation of the assay for propranolol is 4.5% ($n = 6$).

Analysis of pharmacokinetic data

The area under the curve (AUC) was determined using the trapezoidal method. The maximum concentration (C_{max}) and the time to peak plasma concentration (t_{max}) are the observed values. All data are presented as mean ± s.d. Statistical analysis was performed by analysis of variance and the Wilcoxon paired-sample test as appropriate. Differences were considered statistically significant if a two-tailed P value was < 0.05. The Newman-Keuls procedure was used as a method of making multiple comparisons ($\alpha = 0.05$) (Armitage & Berry, 1987).

Results

Co-administration of nicardipine significantly increased C_{max} of propranolol by 80% and increased the area under the curve (AUC) during the first 9 h by 47% (Figure 1). As measurements were only made at 30 min intervals from 60 min after drug ingestion, t_{max} could not be determined with great precision; nevertheless nicardipine tended to reduce time to peak plasma levels of propranolol (109 ± 42 *vs* 86 ± 32 min, NS) (Table 1).

The changes in both systolic and diastolic blood pressure, 2 h after ingestion, tended to be greater in the subjects treated with the combination of propranolol and nicardipine (−18.3% for SBP and −11.8% for DBP), compared with those treated with propranolol alone (−10.1% for SBP and −5.7% for DBP); these differences did not reach statistical significance (Figure 2). The decrease in heart rate 2 h after ingestion was significantly more pronounced in the subjects treated with propranolol alone (−23.5 *vs* −12.4%, $P < 0.05$) (Figure 3). This difference remained statistically significant after allowance was made for multiple comparisons.

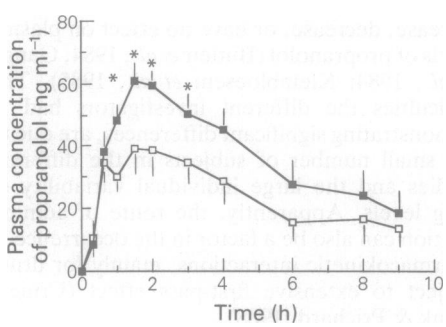

Figure 1 Plasma propranolol concentration-time course after oral administration of propranolol 80 mg with (■) and without (□) nicardipine 30 mg. Mean data (s.d.), $n = 12$; $^*P < 0.05$.

Table 1 Influence of nicardipine on the pharmacokinetics of propranolol; mean ± s.e. mean (* $P < 0.01$)

	Without nicardipine	*With nicardipine*
Propranolol (n = 12)		
t_{max} (min)	109 ± 42	86 ± 32
C_{max} (ng ml^{-1})	72.8 ± 38.8	131.1 ± 65.3*
AUC (0–9) (ng ml^{-1} min)	5.53 ± 3.21	8.14 ± 4.26*

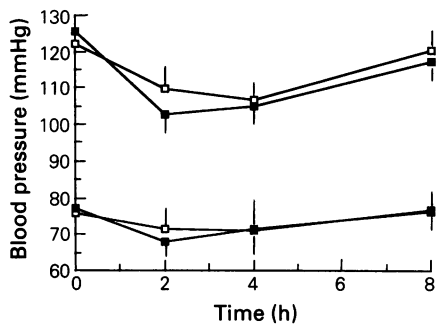

Figure 2 Mean systolic and diastolic blood pressure after administration of propranolol 80 mg with (■) and without (□) nicardipine 30 mg. Mean data (s.d.), $n = 12$.

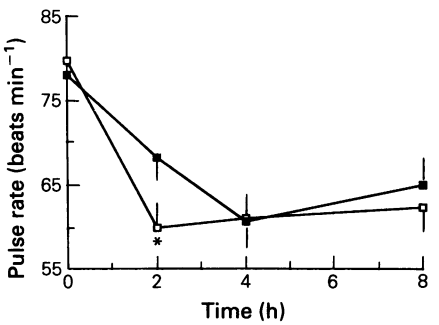

Figure 3 Mean pulse rate after administration of propranolol 80 mg with (■) and without (□) nicardipine 30 mg. Mean data (s.d.), $n = 12$; *$P < 0.05$.

Discussion

In the present study, two changes in single-dose propranolol pharmacokinetics were observed after co-administration of nicardipine. First, a significant increase in the C_{max} value of propranolol was observed. Secondly, there was an increase in the AUC (0–9), indicating an increase in bioavailability. Time to peak plasma levels of propranolol tended to be reduced, although statistical significance was not reached, possibly due to the limited sample size. This increase in bioavailability could result from either an increased absorption from the gastrointestinal tract or decreased hepatic 'first-pass' clearance, or both. However, more than 95% of a single oral dose of propranolol is absorbed from the gastrointestinal tract, this mainly in the small intestine (Shand, 1974). It is therefore unlikely that the increased bioavailability would be the result of increased absorption, related to an increase in mesenteric blood flow (Stone *et al.*, 1980).

A more likely explanation for the increase in AUC is decreased hepatic clearance of propranolol. It is well known that propranolol is a drug with a high hepatic extraction ratio; therefore its hepatic clearance is dependent on hepatic blood flow (Cruickshank & Prichard, 1988). Moreover, propranolol is frequently used in textbooks as an example of a drug following the 'parallel-tube' model of drug elimination (Grahame-Smith & Aronson, 1980). Following this model, and in order to explain the about 50% increase in AUC, hepatic blood flow should decrease by approximately 50%. However, it has been demonstrated that nicardipine increases hepatic blood flow (Sorkin & Clissold, 1987), and therefore three theoretical mechanisms remain.

Calcium antagonists have been reported to reduce the clearance of antipyrine (Bauer *et al.*, 1986), indicating a direct effect of these drugs on microsomal drug oxidating activity. The observed increase in AUC and C_{max} of propranolol, when co-administrated with nicardipine, could thus result from a reduction in intrinsic clearance and hence a decreased 'first-pass' clearance of propranolol. Propranolol is subjected to an extensive 'first-pass' hepatic metabolism, so even minor changes of the oxidative pathway may induce large increases in plasma propranolol levels.

A second possible explanation is offered by the fact that calcium antagonists have been demonstrated to open arterio-venous shunts.

Thus, the co-administration of nicardipine could increase splanchnic and liver blood flow, thus causing a functional shunt in the liver, allowing propranolol to escape partly from its extensive 'first-pass' hepatic metabolism, as proposed to explain similar observations related to the intake of food (Melander *et al.*, 1977).

Thirdly, it has been suggested by some investigators that, for β-adrenoceptor blockers having very high extraction ratios, such as propranolol, there can be saturable first-pass metabolism, resulting in dose-dependent bioavailability (Evans & Shand, 1973). Therefore, the increase in systemic bioavailability of propranolol, induced by nicardipine, could be related to an increased hepatic delivery of propranolol, transiently decreasing its saturable clearance (Evans *et al.*, 1986).

The present results indicate that nicardipine increases the bioavailability of propranolol, probably by decreasing its hepatic clearance, but that pharmacodynamics are little affected. Indeed, blood pressure and heart rate tended to decrease more when propranolol and nicardipine were administered together than when propranolol was given alone, but differences are of doubtful significance. The opposite effects of nicardipine and propranolol on heart rate may explain the smaller fall in heart rate, observed when the drugs are given together.

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