The effect of oral verapamil therapy on antipyrine clearance

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The influence of chronic verapamil treatment on antipyrine elimination was studied in eight angina patients. Antipyrine half-life (mean $\pm$ s.d.) was 13.1 ± 1.15 h at the start of therapy and 16.6 ± 3.05 h ($P < 0.05$) during chronic oral administration of verapamil (80–120 mg four or three times daily for 4 to 7 months). There was a significant decrease in antipyrine clearance (mean $\pm$ s.d, 43.2 ± 16.8 ml min⁻¹ vs 28.7 ± 16.6 ml min⁻¹, $P < 0.01$) while the change of distribution volume was insignificant. Verapamil elimination was also found to be impaired after chronic dosing as compared to single administration. Half-lives measured from the concentration vs time and urinary excretion rate vs time curves were both prolonged and oral clearance was decreased. Our results suggest that the inhibition of drug-metabolizing enzymes accounts for the impairment of verapamil elimination on chronic administration.

Keywords verapamil chronic treatment elimination antipyrine enzyme inhibition

Introduction

Several authors have reported prolonged elimination of verapamil during chronic administration as compared to that following a single dose (Kates *et al.*, 1981; Freedman *et al.*, 1981; Shand *et al.*, 1981; Wagner *et al.*, 1982; Schwartz *et al.*, 1982). Schwartz *et al.* (1985) suggested that a decrease of hepatic blood flow caused by lowering of cardiac output may explain this phenomenon. However, they were unable to show any changes in indocyanine green clearance during chronic verapamil administration. Meredith *et al.* (1985) have found that a single dose of verapamil elevated apparent hepatic blood flow which then fell towards placebo values with continued dosing. An impairment of drug-metabolizing hepatic enzymes is another possibility to account for the observed prolongation of verapamil elimination. To test this hypothesis we studied the kinetics of antipyrine in patients before and during chronic verapamil monotherapy. Antipyrine clearance is a well-established index of a drug-metabolizing capacity in humans and

appears to be sensitive to factors that stimulate or inhibit oxidative metabolism (Vesell, 1979).

Methods

Patients and drug administration

Eight male patients with stable angina pectoris were studied. Their mean age was 51.2 years (range 44–60) and their mean body weight was 80.3 kg (range 72–90). Liver and renal functions were both normal, as assessed by history, physical examination and appropriate laboratory tests. Informed consent was obtained. Two weeks prior to the study the patients did not receive any medication except nitroglycerin sublingually in cases of chest pain. Two hours after a light breakfast each patient was given 80 or 120 mg verapamil (Finoptin® tablets, Orion Pharmaceutica, Finland) and 1 g antipyrine in 100 ml of water. Blood samples were obtained at 0, 0.5,

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1, 1.5, 2, 3, 4, 6, 8, 10 and 24 h thereafter. Serum was separated and stored at -18°C until analysis. Total urine was collected by spontaneous micturition during 48 h; the volume of each specimen was recorded and an aliquot was stored at -18°C . All patients were then discharged on chronic verapamil therapy for 4–7 months. Each subject received the same dose as in the single-dose study every 6 or 8 h. The pharmacokinetic study was repeated following the final verapamil dose according to the same protocol as above (including antipyrine).

Drug assays

Serum and urine concentrations of verapamil were measured using cation-exchange high performance liquid chromatography (Piotrovskii *et al.*, 1983). Serum concentrations of antipyrine were measured by reversed-phase liquid chromatography (Elman *et al.*, 1984).

Pharmacokinetic calculations

Serum half-lives ($t_{1/2s}$) were calculated from the slopes of the terminal log-linear sections of the serum drug concentration vs time plots by least squares linear regression. Urine half-lives of verapamil ($t_{1/2u}$) were calculated in the same way using the log-linear sections of the urinary drug excretion rate vs time plots. Excretion rate was calculated as the amount of verapamil in each urine specimen divided by the corresponding time interval and was related to the midpoint of this interval. Antipyrine clearance (CL) was calculated as $0.693(\text{Dose}/C(0))t_{1/2s}$, where $C(0)$ is the extrapolated serum antipyrine concentration at $t = 0$. $C(0)$, together with $t_{1/2s}$, were estimated by linear regression assuming that antipyrine kinetics are monoexponential. The apparent volume of distribution of antipyrine

was calculated from $\text{Dose}/C(0)$. Verapamil oral clearance (CL_{po}) after a single dose was calculated as Dose/AUC , and on a chronic dosing as $\text{Dose}/\text{AUC}(\tau)$, where τ is a dosage interval (6 or 8 h). AUC and $\text{AUC}(\tau)$ were estimated using the trapezoidal rule with extrapolation to infinity for the former.

The results are presented as arithmetic mean $\pm$ s.d. Data were compared by Student's paired *t*-test.

Results

The findings of the study are summarized in Table 1 and Figure 1. Verapamil oral clearance during long-term treatment was 2.3 times ($P < 0.01$) lower than that following a single dose. Verapamil half-life was significantly ($P < 0.02$) prolonged, and it is noticeable that $t_{1/2s}$ did not differ significantly from $t_{1/2u}$ after both single and chronic administration. Antipyrine half-life was substantially prolonged on chronic verapamil dosing and this was almost exclusively due to a lowering of its clearance (see Figure 1) since the apparent volume of distribution was unchanged. No correlations were found between verapamil CL_{po} and $t_{1/2s}$ values after single and chronic dosing with those of antipyrine. Correlation coefficients for verapamil and antipyrine clearances were -0.089 and 0.084 , whereas those between half-lives were 0.185 and 0.124 for single and chronic administration, respectively.

Discussion

Our data confirm that the oral clearance of verapamil is lowered during chronic treatment (Freedman *et al.*, 1981; Kates *et al.*, 1981; Shand *et al.*, 1981; Schwartz *et al.*, 1982, 1985; Eichel-

Table 1 Pharmacokinetic characteristics of verapamil and antipyrine after a single verapamil dose and during chronic therapy ($n = 8$)

	Single dose	Chronic treatment	P
<i>Verapamil</i>			
CL_{po} (1 min^{-1})	3.21 ± 1.19	1.26 ± 0.58	<0.01
$t_{1/2s}$ (h)	6.60 ± 1.33	9.38 ± 2.15	<0.02
$t_{1/2u}$ (h)	7.18 ± 3.37	10.40 ± 3.95	<0.05
<i>Antipyrine</i>			
CL (ml min^{-1})	43.2 ± 16.8	28.7 ± 16.6	<0.01
$t_{1/2}$ (h)	13.1 ± 1.15	16.6 ± 3.05	<0.05
$V(1)$	47.7 ± 5.1	39.5 ± 8.1	NS

Figure 1 Individual values of antipyrine clearance after a single and chronic dosing of verapamil (○). Closed circles and bars show mean values and s.d., respectively.

baum *et al.*, 1984; Meredith *et al.*, 1985). The mean relative reduction was 2.3 in our subjects, and this value is very close to that computed from the data compiled by Wagner *et al.* (1982).

It has been suggested that the observed clearance change is only apparent inasmuch as it reflects the presence of a 'deep' tissue compartment for verapamil which is not detected from single dose data owing to the limitation of assay sensitivity. However, in the present study verapamil half-lives calculated from urinary excretion data collected over 48 h were not significantly longer than those calculated from plasma data collected for only 24 h.

Two other explanations for the prolongation of verapamil elimination during chronic treatment are theoretically possible: a decrease in hepatic blood flow and an inhibition of the enzymes responsible for verapamil metabolism. The first hypothesis contradicts the data by

Schwartz *et al.* (1985) and Meredith *et al.* (1985) which have shown that chronic treatment with verapamil did not change indocyanine green clearance reflecting hepatic blood flow. Our finding that antipyrine clearance decreased during long-term verapamil treatment by 66% supports the second suggestion since the oral clearance of antipyrine depends directly upon the activity of hepatic oxidases (Vesell, 1979) and is independent of liver blood flow. Verapamil is eliminated mainly by oxidative metabolism in the liver (McIlhenny, 1971). In contrast to antipyrine verapamil has a high hepatic clearance. However, theory predicts that its oral clearance should also be dependent on the activity of hepatic enzymes. Autoenzyme inhibition may be caused by verapamil itself or by its metabolites. Renton (1985) has shown that verapamil inhibits cytochrome P-450-dependent biotransformation of other drugs *in vitro*.

Wagner (1984) has proposed that the prolongation of verapamil elimination during chronic treatment can be explained by saturable drug metabolism. In this case verapamil oral clearance should be dose- and (mean) input rate-dependent. However, this was not found for single (McAllister & Kirsten, 1982) nor for multiple (Frishman *et al.*, 1982; Anderson *et al.*, 1982) administration of drug doses routinely used in clinical practice. AUC values after single doses and steady-state verapamil plasma concentration during chronic treatment are linearly dependent upon dose size or dosing rate.

We suggest that prolonged verapamil elimination during chronic administration results mainly from the impairment of its metabolism caused by auto-enzyme inhibition. Thus, the elimination of other drugs subject to hepatic oxidative metabolism may also be altered when they are used concomitantly with verapamil. Examples of such interactions are known in the literature (Pasanisi *et al.*, 1984; Macphree *et al.*, 1986).

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