An investigation of the cause of accumulation of verapamil during regular dosing in patients

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The accumulation of verapamil during regular dosing conditions was studied. Plasma concentrations of verapamil (V) and norverapamil (NV) were measured as were urinary concentrations of verapamil, norverapamil, and four other *N*- and *O*-dealkylated metabolites in nine patients after an initial single dose and after chronic oral verapamil administration to steady-state plasma concentrations. Indocyanine green (ICG) clearance was determined immediately prior to the initial verapamil dose and prior to the verapamil washout from regular dosing. An approximately two-fold accumulation of V had occurred during regular dosing. The area under the plasma concentration-time curve (AUC_1) after the first dose was $417.4 \pm 276.7 \text{ ng ml}^{-1} \text{ h}$ (mean $\pm$ s.d.) and increased to $786.5 \pm 54 \text{ ng ml}^{-1} \text{ h}$ ($P < 0.01$) during one dosage interval at steady-state (AUC_{ss}). NV also tended to accumulate from an AUC_1 of 552.6 ± 411 to an AUC_{ss} $668.7 \pm 332 \text{ ng ml}^{-1} \text{ h}$ ($P < 0.09$). The ratio of $AUC\text{-V}$ to $AUC\text{-NV}$ was unchanged. The verapamil elimination half-life ($t_{1/2}$) increased from 8.4 ± 4.2 to $12.0 \pm 3.6 \text{ h}$ ($P < 0.01$) whereas the norverapamil $t_{1/2}$ was unchanged. ICG clearance was unchanged. Urinary excretion of NV increased slightly but the ratio of urinary V/NV concentrations was not significantly altered nor was the ratio of four other metabolites to verapamil or the ratio of the combined *o*-demethylated to the *N*-dealkylated metabolites. These results suggest that verapamil accumulation during regular dosing is not the result of changes in hepatic blood flow but is due either to impaired clearance during repeated dosing or to the presence of a deep tissue compartment of drug distribution which is not detected after single doses.

Keywords verapamil steady-state accumulation kinetics

Introduction

Several investigators have reported an increased verapamil elimination half-life during chronic oral drug administration as compared to that measured after a single oral dose (Freedman *et al.*, 1981; Kates *et al.*, 1981; Schwartz *et al.*, 1982; Shand *et al.*, 1981; Wagner *et al.*, 1982). Possible explanations for such a finding include (a) nonlinear pharmacokinetics, (b)

changes in hepatic blood flow during chronic dosing leading to changes in first-pass hepatic drug extraction, (c) metabolite inhibition of parent drug biotransformation, (d) alteration in the differential first-pass metabolism of the (+)- and (–) isomers, and/or (e) the presence of a deep tissue compartment not easily detected after single doses. This study was designed to

investigate potential factors responsible for altered verapamil elimination.

Methods

Study population

Nine patients (eight male and one female) with a mean age of 58 (range 30–67) years and mean weight of 94 (range 66–135) kg were studied. Verapamil was administered for management of supraventricular arrhythmias in four and chest pain syndromes in five. New York Heart Association Functional Classification ranged from I to III (average = II). Other medications held constant during this study included nitrates in four, β -adrenoceptor antagonists in three, diuretics in three, digitalis in two, aminophylline in one, and insulin in one.

Written informed consent was obtained and subjects were admitted to the General Clinical Research Centre of The Methodist Hospital. After an overnight fast, an intravenous indocyanine green clearance (ICG) test was performed by rapid injection of 0.5 mg/kg ICG with 5 ml blood samples at 3, 5, 8, 10, 12 and 15 min. In eight of nine patients, 80 mg verapamil tablets were then given orally and 5 ml blood samples were obtained at 0, 0.25, 0.3, 0.33, 0.42, 0.5, 0.67, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 14, 20 and 24 h after dosing. Total urinary output during this period was collected in 6 h aliquots. One patient received a 40 mg dose of verapamil in capsule form. Data from this patient are presented but excluded from the group data analysis due to possible differences in drug absorption secondary to the different formulation administered. Plasma samples and urinary aliquots were stored at -15°C until assay.

After a minimum of 72 h of oral verapamil dosing (80 mg in eight patients and 40 mg in one patient) every 6 h, the ICG test was repeated, the same dose of verapamil was again administered and blood and urine samples were collected at the same time intervals as after the first dose.

Drug assays

Plasma samples were analyzed for verapamil and norverapamil concentration using gas-liquid chromatography with nitrogen-phosphorus detection (Abernethy *et al.*, 1984). Urine samples were analyzed for verapamil and five of its major *O*-demethylated and *N*-dealkylated metabolites (norverapamil, D617 = 2-(3,4-dimethoxyphenyl)-5-methanlamino-2-isopropylvaleronitrile, PR25 = 2-(4hydroxy-3-methoxyphenyl)-5-

methlamino-2-isopropylvaleronitrile, D620 = 5-amino-2-(3,4-dimethoxyphenyl)-2-isopropylvaleronitrile and PR22 = 2-(4-hydroxy-3-methoxyphenyl)-8-(3, 4-dimethoxyphenyl)-2-isopropyl-6-methoxyphenyl)-8-(3, 4-dimethoxyphenyl)-2-isopropyl-6-azaocitanitrile using a minor modification of the high performance liquid chromatographic method described by Kuwada *et al.* (1981).

Indocyanine green concentration was determined using a Beckman spectrophotometer with optical densities read at 805 nm to determine percent absorbance which was converted to plasma concentration by the use of ICG standard. ICG disappearance rate was determined by least squares regression over the log-linear phase from 5 to 12 min (Martin *et al.*, 1975).

Pharmacokinetic calculations

The areas under the concentration-time curves (AUCs) were estimated by the linear trapezoidal rule and the extent of drug accumulation (AR) calculated according to the equation:

$$\text{AR} = \frac{\text{AUC}_{\text{ss}0-6}}{\text{AUC}_{10-\infty}}$$

where $\text{AUC}_{\text{ss}0-6}$ is the AUC at steady-state between 0 and 6 h (one dosing interval) and $\text{AUC}_{10-\infty}$ the AUC after the first dose extrapolated to infinity (Gibaldi *et al.*, 1975). Apparent oral verapamil clearance was estimated by dose/AUC. Drug elimination half-life ($t_{1/2}$) was estimated by least-squares regression analysis of the log-linear portion of the concentration-time curve (from 6–24 h in most subjects).

All values presented are the mean $\pm$ s.d. Paired data were compared by the Student's paired *t*-test for statistical significance (defined as $P < 0.05$).

Results

Verapamil and norverapamil concentrations during oral verapamil administration

The verapamil and norverapamil plasma concentration data following the first and steady-state doses for the nine patients are shown in Figure 1 and Table 1. As in the previous studies, verapamil accumulated during regular dosing. The mean $\text{AUC}_{0-\infty}$ for the first verapamil dose was $417 \pm 277 \text{ ng ml}^{-1} \text{ h}$ and the AUC for one dosing interval during regular dosing was $787 \pm 511 \text{ ng ml}^{-1} \text{ h}$ ($P < 0.01$) yielding an accumulation ratio of 1.88. The AUC for norverapamil showed a similar, but

Figure 1 Plasma concentration time data for verapamil (○) and norverapamil (●) in the nine patients after the first dose (---) and after the steady-state dose (—).

not quite statistically significant, trend ($\text{AUC NV}_1 = 553 \pm 411 \text{ ng ml}^{-1} \text{ h}$ to $\text{AUC NS}_{ss} = 669 \pm 332 \text{ ng ml}^{-1} \text{ h}$, $P < 0.09$). Since norverapamil accumulated to a lesser extent there was a slight increase in the ratio of $\text{AUC verapamil}/\text{AUC norverapamil}$ for the first vs the steady-state dose, but this was not statistically significant. The verapamil $t_{1/2}$ increased from $8.4 \pm 4.2 \text{ h}$ to $12 \pm 3.6 \text{ h}$ ($P < 0.01$). Norverapamil $t_{1/2}$ was not significantly altered (9.6 ± 3.4 vs $10.4 \pm 1.5 \text{ h}$).

Indocyanine green clearance was not significantly changed during verapamil administration ($\text{ICG}_1 5.8 \pm 2.2$ vs $\text{ICG}_{ss} 6.3 \pm 2.5 \text{ ml}^{-1} \text{ min}^{-1} \text{ kg}$).

The ratios of urinary verapamil excretion to that of each of the 5 metabolites were compared after the first vs steady-state dose as were the ratios of the *O*-demethylated to the *N*-dealkylated metabolites (Table 1). The only trend noted was a decrease in the V/NV ratio from 0.96 ± 0.55 to 0.47 ± 0.25 during chronic verapamil therapy ($P < 0.09$). No significant changes in the

relative proportions of other urinary metabolites were noted.

Discussion

This study confirms the accumulation of verapamil during regular oral dosing. This finding has been uniform in patients of widely varying ages receiving differing verapamil doses for a wide spectrum of cardiovascular diseases (Freedman *et al.*, 1981; Kates *et al.*, 1981; Schwartz *et al.*, 1982; Shand *et al.*, 1981; Wagner *et al.*, 1982). The factors responsible for this phenomenon have not previously been explored.

Verapamil has a high hepatic extraction ratio and some or all factors involved in the extent of hepatic first pass extraction including hepatic blood flow, efficiency of hepatic drug extraction, and hepatic oxidative drug metabolizing capacity may therefore be altered during chronic oral

Table 1 Kinetic data from oral verapamil studies (mean $\pm$ s.d.)

	<i>Dose 1</i>	<i>Regular dosing</i>	
AUC-V (ng ml ⁻¹ h)	417 $\pm$ 277	786 $\pm$ 511	$P < 0.01$
AUC-NV (ng ml ⁻¹ h)	533 $\pm$ 411	689 $\pm$ 332	$P < 0.09$
AUC-V/AUC-NV	0.9 $\pm$ 0.5	1.1 $\pm$ 0.2	NS
V $t_{1/2}$ (h)	8.4 $\pm$ 4.2	12.1 $\pm$ 3.6	$P < 0.01$
NV $t_{1/2}$ (h)	9.6 $\pm$ 3.4	10.4 $\pm$ 1.5	NS
ICG clearance (ml min ⁻¹ kg ⁻¹)	5.8 $\pm$ 2.2	6.3 $\pm$ 2.5	NS
Urinary V/NV excretion†	0.96 $\pm$ 0.55	0.47 $\pm$ 0.25	$P < 0.09$
Urinary V/D617 excretion†	0.28 $\pm$ 0.2	0.20 $\pm$ 0.12	NS
Urinary V/D620 excretion†	0.58 $\pm$ 0.45	0.34 $\pm$ 0.27	NS
Urinary excretion of N-dealkylated/ O-demethylated metabolites†	0.2 $\pm$ 0.11	0.18 $\pm$ 0.1	NS

AUC = area under the time vs concentration curve; V = verapamil;
 NV = norverapamil, $t_{1/2}$ = elimination half-life; ICG = indocyanine
 green;

NS = nonsignificant; † = urinary excretion from 0–6 h.

administration. The AUC for verapamil during regular dosing was significantly increased when compared to that seen after the first dose and thus the apparent oral clearance was decreased. The $t_{1/2}$ for verapamil increased from 8.4 ± 4.2 to 12 ± 3.6 h without alteration in the norverapamil $t_{1/2}$. The AUC verapamil/AUC norverapamil ratio tended to increase, though this increase did not reach statistical significance. Similarly, the relative urinary excretion ratios of verapamil to its metabolites were not statistically different.

This suggests the prolongation of verapamil $t_{1/2}$ was not due to impaired verapamil hepatic biotransformation resulting in decreased metabolite formation and total urinary metabolite clearance. The metabolites measured account for 70–80% of total metabolite formation in man (Kuwada *et al.*, 1981). We cannot exclude the possibility of inhibition of formation of the metabolites which were not evaluated in this study; however they account for a minor proportion of total verapamil turnover in man. Therefore, even total inhibition of these routes of verapamil biotransformation during chronic dosing cannot explain the marked prolongation in verapamil $t_{1/2}$. This indirect evidence of unchanged verapamil clearance during chronic

dosing is supported by the work of Eichelbaum (1980) and Eichelbaum *et al.* (1980, 1982) in which little change ($< 20\%$) in verapamil elimination $t_{1/2}$ was noted when deuterium labelled verapamil was administered to six normal subjects on days 2, 8, 16, and 21 of oral verapamil dosing. Both of these lines of evidence suggest that verapamil clearance is not significantly altered during chronic dosing.

Unchanged ICG clearance before and during chronic verapamil administration indicate that no dramatic change in hepatic blood flow occurred. Therefore altered hepatic first-pass extraction of verapamil during chronic administration is not likely. The presence of a deep tissue compartment into which verapamil distributes that cannot be detected with current analytical methodology cannot be ruled out. During chronic dosing in which significant drug accumulation occurs, such a compartment would become identifiable by the terminal phase of drug elimination, and would result in prolongation of the observed $t_{1/2}$.

Our pharmacokinetic observations with verapamil have important clinical implications. It has been shown that increasing serum concentrations of verapamil produce increasing prolongation of the P–R interval (Eichelbaum

et al., 1980; Keefe *et al.*, 1981), increasing suppression of both resting and exercise heart rates in atrial fibrillation (Schwartz *et al.*, 1981), and increasing peripheral vasodilatation (Angus *et al.*, 1976). In addition, verapamil's direct myocardial depressant effect becomes magnified at higher doses or in the presence of depressed left ventricular function (Angus *et al.*, 1976). Our findings suggest that in order to produce the desired serum concentration and response and to minimize unwanted or toxic drug effects during chronic verapamil administration, verapamil doses should be given less frequently or in smaller doses than previously suggested by single dose studies.

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