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Short Communication

Comparative bioavailability of verapamil from rapidly absorbed and slow release preparations*

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Introduction

Verapamil, a calcium channel blocker, is used as an antianginal agent and for the treatment of supraventricular tachyarrythmias and arterial hypertension. Orally administered verapamil is almost completely absorbed from gastrointestinal tract, but much of the drug undergoes presystemic metabolism in the liver (first-pass metabolism). Hence, the systemic bioavailability of orally administered verapamil is only 10–35% [1–6].

Although the $R(+)$ isomer of verapamil is less potent as a cardiodepressant compared with $S(-)$ isomer [7–9], both isomers are equipotent with regard to their coronary vasodilatory effects. For this reason verapamil is manufactured and administered as a racemic mixture. Therapeutic range for verapamil of 50–400 $\mu g\ m^{-1}$ which depends on the disease, is derived from the sum of both enantiomers [10–13].

Due to the high degree of first-pass metabolism, the possibility of non-linear kinetics for verapamil has been mentioned by several authors [5, 6, 14–16]. In those studies, a 2–3 times higher level of verapamil was found at steady-state compared with a single dose. The non-linear kinetics may be caused by the influence of dose as well as different form of drug, i.e. rapidly absorbed (RA) and slow release (SR) on the bioavailability and pharmacokinetics of verapamil. The aim of this study was to compare verapamil bioavailability from RA and SR preparations and to investigate the influence of dose-related effects.

Materials and Methods

Subjects

Rapidly absorbed preparations containing 80 and 120 mg and an SR preparation containing 120 mg of verapamil were used. The study was carried out on 72 patients divided into three groups. Group I (24 patients) and group II (24 patients) were ingested by RA preparation of verapamil using 80 and 120 mg doses, respectively. The patients of group III (24 patients) have received twice daily (every 12 h) 120 mg of verapamil in the SR form preparation.

Procedure

Blood samples were collected for a period of 24 h (single dose) or 12 h (steady state) after the drug administration. Serum concentrations of verapamil were assayed using a liquid chromatography method with fluorescence detection. To 1.0 ml of serum sample were added 0.2 ml of 2 M NaOH and 4 ml of *n*-heptane. Extraction was made by gentle automated shaking for 15 min. After centrifugation, 3.5 ml of organic phase was transferred to a conical tube and evaporated to dryness in a water-bath at 40°C under a stream

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of air. The extract was redissolved in 200 μl of mobile phase. An aliquot of 20 μl was injected into the chromatographic column.

Chromatography

Chromatographic analysis was performed on a Pye-Unicam 4000 liquid chromatograph equipped with Shimadzu fluorimetric detector model RF-530. The column was Partsil 10 μm PAC (Pye Unicam Ltd), a mobile phase of methanol–water–glacial acetic acid–triethylamine (65:35:0.5:0.1, v/v/v/v) was used at a flow rate of 1.0 ml min^{-1}. The detector was set to 278 nm excitation and 320 mn emission wavelengths. Analysis was performed at ambient temperature. Representative chromatograms of a drug-free serum sample, and verapamil-spiked serum sample are shown in Fig. 1.

The concentration of verapamil in the samples was calculated from peak heights using the slope and intercept calculated by linear regression analysis of the calibration curve data, made each day of analysis.

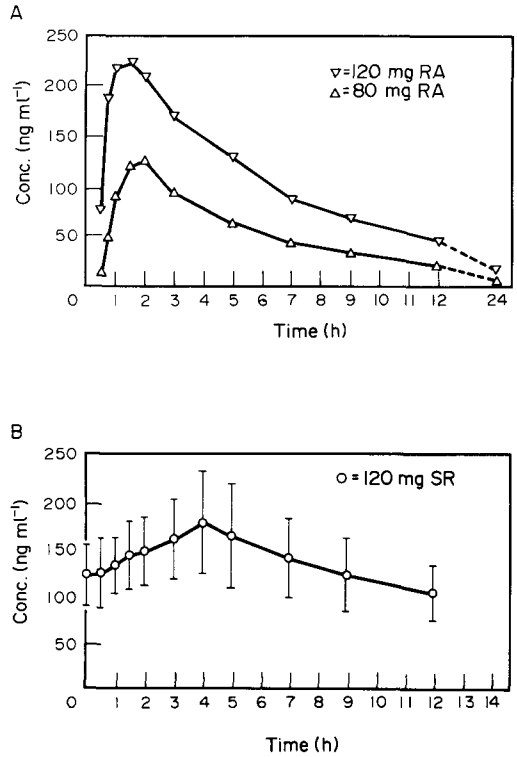

Figure 1
Chromatograms of serum sample: drug-free (A), and spiked by 50 ng of verapamil (B).

Results and Discussion

The standard curve for verapamil in the aforementioned method was linear over a range 20–400 ng ml^{-1}. The detection limit was 5 ng ml^{-1}. The calibration curves for verapamil concentration, ranging from 20 to 200 ng ml^{-1}, were drawn at each day of investigations. Correlation coefficient of those curves ranged from 0.9991 to 0.9945. Standard curve intercepts were not significantly different from 0 ($P > 0.05$) for all curves, including negligible interference from endogenous compounds. During the analytical assays, the precision and reproducibility of the method was calculated from the RSDs of the slopes for each data point to be from 4.13 to 8.85% (in-day variability). The reproducibility of the method was defined as RSDs of the peak heights taken from each curve (intra-day variability). The numerical values for reproducibility are listed in Table 1. The average recovery of the analysis was 91.07%.

Table 1
Numerical values for reproducibility of the analytical method

Conc. (ng ml^{-1})	Conc. determined (±SD)	RSD (%)
20	21.24 ± 1.73	8.14
50	49.50 ± 2.10	4.23
100	99.49 ± 3.34	3.36
150	148.04 ± 5.49	3.71
200	201.70 ± 3.94	1.96
250	256.12 ± 2.63	1.03

The results obtained *in vivo* (Fig. 2, Table 2) confirm the influence of the dose on the bioavailability of verapamil. An increase of the dose from 80 to 120 mg of RA-preparations produced disproportional increase of basic bioavailability parameters: AUC and C_{max}. The ratios $AUC^{RA}_{120}/AUC^{RA}_{80} = 2.052$ and $C_{max120}^{RA}/C_{max80}^{RA} = 2.092$ indicate, that increasing the dose by 50% produced about a two-fold increase in the AUC and C_{max} values. The third bioavailability parameter (t_{max}) did not change when the dose was increased. Simultaneously, the lack of significant differences in parameters describing elimination of the drug from the body, i.e. elimination rate constant (λ) and half-life ($t_{0.5}$) was observed. Hence, non-linear changes in AUC^{RA} and C_{max}^{RA} values concerning the absorption phase are probably caused by changes in first-pass metabolism, as a result of saturation of enzymes taking part in first-pass metabolism.

Table 2
Parameters of bioavailability of verapamil

Parameter	Dose-preparation 80 mg RA	120 mg RA	120 mg SR
AUC (ng h ml^{-1})	946.5 ± 354.4	1943.0 ± 649.4	1641.0 ± 429.0
C_{max} (ng ml^{-1})	140.1 ± 53.8	293.1 ± 133.7	189.5 ± 50.5
t_{max} (h)	1.68 ± 0.48	1.71 ± 0.94	3.48 ± 118
λ (h^{-1})	0.1004 ± 0.0326	0.0921 ± 0.0132	—
$t_{0.5}$ (h)	7.44 ± 1.86	7.68 ± 1.12	—

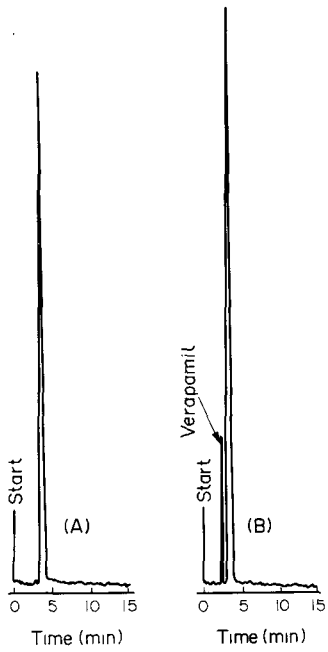

Figure 2
Concentration–time curves of verapamil after single oral dose of 80 mg RA, 120 mg RA (A), and after chronic ingestion of 120 mg SR twice daily (B).

Moreover, prolongation of drug release (SR-preparation) diminishes the bioavailability to about 15% in comparison with the same dose in the RA-preparation. This phenomenon can be explained by more efficient metabolism during the absorption of the slower released formulation (SR).

Conclusions

The analytical method described here is useful for pharmacokinetic studies and therapeutic drug monitoring, due to its high sensitivity, specificity and reproducibility. Using this method, lack of linear increase of concentration and some pharmacokinetic parameters with the dose of verapamil has been found. The non-linear relationship between the dose and concentration and, as a consequence, between dose and clinical effect should be taken into consideration to avoid unexpected side effects.

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