Pharmacokinetics of conventional and slow-release verapamil

F. FOLLATH, H. R. HA, EVELYNE SCHÜTZ & F. BÜHLER

Division of Clinical Pharmacology, Department of Medicine, University Hospital (Kantonsspital), Basel, Switzerland

1 Verapamil is a racemic mixture of two optical isomers, the (–)-form being the more active component. Recent studies indicate a rapid hepatic transformation of (–)-verapamil, which results in different concentration–effect relationships after oral and intravenous administration. In practice the important pharmacokinetic properties of verapamil are low bioavailability (20%), predominant elimination by metabolism (> 95%) and a relatively short half-life ($t_{1/2\beta}$ is 3–5 h). After repeated dosing, the rate of hepatic drug clearance seems to decrease.

2 Slow release (SR) formulations of verapamil may offer certain therapeutic advantages during long-term treatment. A comparison of conventional (C) and SR tablets in a 1-week treatment of eight cardiac patients showed a relative bioavailability (AUC_{SR}/AUC_C) of $90 \pm 30\%$. More stable serum drug levels were maintained by 12-hourly administration of SR verapamil.

3 A further study using a new 240 mg SR preparation in patients with arterial hypertension showed that even a single daily dose can be sufficient for adequate blood pressure control over 24 h.

Keywords verapamil slow release formulation pharmacokinetics

Introduction

The elucidation of basic pharmacokinetic properties of verapamil has made an important contribution to its improved therapeutic use during the last few years. Today, it is clear that initial doubts about the value of the oral preparation (Krikler, 1974) were a consequence of unrecognized hepatic first-pass metabolism that often results in inadequate drug levels at doses below 80–120 mg. Differences in concentration–effect relationships after intravenous and oral administration can now be explained by stereoselective verapamil metabolism. Further useful information has been gained from studies of verapamil elimination in patients with hepatic and cardiac diseases. The essential data required to define optimum dosage regimens for the various therapeutic indications are available. In this paper the clinically relevant pharmacokinetic properties of verapamil are reviewed and new data are presented on verapamil slow-release formulations.

Pharmacokinetics of verapamil

Orally ingested verapamil is well absorbed, but only about 20% of the dose will reach the systemic circulation as unchanged substance (Schomerus *et al.*, 1976). This low bioavailability is due to rapid drug uptake and metabolism by liver cells. A high first-pass hepatic extraction (0.84–0.89) could be directly demonstrated in cardiac patients during diagnostic catheterization by comparison of verapamil concentrations in blood samples from the ascending aorta and hepatic veins (Woodcock *et al.*, 1981b). Another interesting aspect of verapamil pharmacokinetics is the stereoselectivity of verapamil biotransformation. The clinically used racemic mixture contains equal amounts of (+)-verapamil and (–)-verapamil, which is 8–10 times more active (Raschack *et al.*, 1976). Utilizing a stable isotope technique Vogelgesang *et al.* (1984) could show that the bioavailability of (+)-verapamil in healthy volunteers is about 50% and that of (–)-verapamil

only 20%. The more rapid biotransformation of the active component explains why at a given serum verapamil concentration, measured by the standard h.p.l.c. methods, the intravenously administered drug appears to prolong PQ-intervals more than the oral preparation (Reiter *et al.*, 1982). If concentration-effect relationships are based on specific measurements of (–)-verapamil alone, the influences on AV-conduction become independent of the route of administration (Eichelbaum *et al.*, 1980). Unfortunately, such stereoselective measurements cannot be routinely carried out in most laboratories and, therefore, present efforts to define optimum serum concentration ranges for the different therapeutic indications are likely to remain unsuccessful.

The elimination of verapamil from the organism occurs nearly exclusively by flow-dependent hepatic metabolism. Interestingly enough, verapamil clearance during repetitive oral administration is lower than after single doses (Shand *et al.*, 1981, Freedman *et al.*, 1981). Consequently, bioavailability and elimination half-life may increase. Eichelbaum & Somogyi (1984) also found a higher bioavailability after a three week treatment than following the initial test dose (32.8% vs 20.3%), but in their five healthy volunteers $t_{1/2}$ did not change significantly. The mechanism of clearance reduction remains uncertain, inhibitory effects of metabolites, decrease in liver blood flow or dose-dependency of biotransformation must be considered.

Of practical importance are investigations of verapamil pharmacokinetics in patients with renal, hepatic or cardiac diseases. Since less than 5% of verapamil is eliminated as unchanged drug in the urine and metabolites have only a slight (norverapamil) or no pharmacological activity (Neugebauer, 1978), no dosage modification will be required in patients with abnormal renal function. In contrast, verapamil elimination can be substantially altered in patients with liver disease. Somogyi *et al.* (1981) reported a decrease in verapamil clearance by about 50% and a fourfold prolongation of $t_{1/2}$ (mean 14.2 h) in seven cases with liver cirrhosis. Bioavailability was also increased to an average of 52.3% and, thus, the area under the serum concentration curve was 4–5 times higher than in healthy subjects. To avoid unwanted effects the initial doses of verapamil in patients with liver disease should be halved when the drug is injected intravenously, and reduced to one fourth when oral treatment is given.

Despite a lack of specific data, a decreased verapamil clearance has to be expected in patients with congestive heart failure. Woodcock *et al.*

(1981a) observed a 50% clearance reduction in two intensive care patients with low cardiac index and Kates *et al.* (1981) found prolonged $t_{1/2}$ values up to 15 h in patients with chronic atrial fibrillation and heart failure. Well controlled studies to quantify the influence of haemodynamic changes on verapamil kinetics have, to the best of our knowledge, not been carried out. In view of its negative inotropic effect, verapamil should be used with caution in patients with abnormal cardiac function.

Pharmacokinetics of slow-release verapamil

Duration of action following oral administration of verapamil in patients with normal liver function is limited to 6–8 h (Follath *et al.*, 1980). Slow release preparations allowing longer dosage intervals could, therefore, be useful for long-term therapy. We have evaluated the pharmacokinetic properties of two such verapamil formulations.

Methods

Studies were carried out in two groups of patients.

(1) Eight hospitalized cardiac patients (age 63–83 years) were receiving conventional verapamil orally 80 mg three times daily for supraventricular arrhythmias. After 7–10 days repeated blood samples were obtained during a dosage interval (immediately before, 1, 2, 4 and 8 h after the morning dose). The treatment was then continued with a commercially available slow-release verapamil preparation (Isoptin retard®) at a dose of 120 mg 12-hourly. On the seventh day blood sampling was again carried out during a 12-h dosage interval (0, 1, 2, 4, 8 and 12 h).

(2) Eight ambulatory hypertensive patients (age 41–70 years) were treated for 4 weeks either with 120 mg SR-verapamil (Isoptin retard®) twice daily or with a single daily dose of a new 240 mg SR-verapamil preparation. At the end of this period repeated blood samples were obtained and blood pressure measured simultaneously during a study day in hospital. Thereafter, patients were crossed over to the other SR-verapamil formulation and followed for another 4 weeks. They were then studied a second time with repeated blood sampling and blood pressure measurements (immediately before, 2, 4, 8, 12 and 24 h after a maintenance dose).

Measurements of verapamil and norverapamil concentrations in serum were performed with an h.p.l.c. technique (coefficient of variation < 5%, lower limit of detection 2 ng ml⁻¹).

Relative bioavailability of the 120 SR-verapamil preparation (Isoptin retard®) was evaluated by comparing the dose corrected AUC values during a dosage interval with those of the conventional 80 mg verapamil tablets. Statistical differences between trough and peak levels were calculated by the paired *t*-test.

Results

Study I

Serum concentration curves of verapamil and norverapamil during the two successive treatment periods are shown in Figure 1. Average drug concentrations on slow-release and conventional verapamil were comparable ($223.6 \pm 177.7 \text{ ng ml}^{-1}$ vs $280.6 \pm 266.3 \text{ ng ml}^{-1}$ NS), whereas the differences between peak and trough values were significantly smaller on slow-release verapamil ($38.5 \pm 27.5 \text{ ng ml}^{-1}$ vs $244.6 \pm 165.2 \text{ ng ml}^{-1}$, $P < 0.01$). Although absolute verapamil concentrations varied markedly among individual patients, more stable verapamil concentration curves were seen with SR-verapamil in all patients (Figure 2). Relative bioavailability of the 120 mg SR-verapamil tablets amounted to $90 \pm 30\%$. Therapeutic effects in patients with supraventricular arrhythmias were maintained during the treatment period with SR-verapamil.

Study II

Serum verapamil concentrations during prolonged treatment with the two SR-preparations in eight hypertensive patients are shown in Figure 3. Concentration curves during treatment with 120 mg twice daily (Isoptin retard®) were again remarkably stable ($C_{\max} - C_{\min} 32.2 \pm 21.4 \text{ ng ml}^{-1}$), but average concentrations were only $62 \pm 38.2 \text{ ng ml}^{-1}$. Once daily administration of the newer 240 mg SR-verapamil formulation produced a greater variability between trough and peak concentrations ($126.7 \pm 90.6 \text{ ng ml}^{-1}$), but verapamil levels at the end of the 24 h dosage interval remained in the same range as with 120 mg twice daily. With a single exception blood pressure reduction below 160/95 mm Hg was maintained during the whole treatment period. These data are presented in another paper in this volume (Müller *et al.*, 1986).

Discussion

The pharmacokinetic evaluation of two different slow-release verapamil formulations shows several potential advantages over the conventional oral product. Under steady-state conditions the relative bioavailabilities are comparable, while differences between peak and trough concentrations are considerably less with SR-vera-

Figure 1 Serum concentration-time curves for verapamil (○) and norverapamil (●) after (a) 80 mg verapamil and (b) 120 mg SR verapamil (mean $\pm$ s.e. mean, $n = 8$).

Figure 2 Serum concentrations of verapamil in individual patients after (a) 80 mg verapamil and (b) 120 mg SR verapamil.

Figure 3 Serum concentrations of verapamil in individual patients during prolonged treatment with (a) SR verapamil 240 mg once daily and (b) SR verapamil 120 mg twice daily.

pamil. Depending on the therapeutic indication twice, or even once daily administration may be possible. In our patients with supraventricular arrhythmias 120 mg SR-verapamil twice daily maintained a good heart rate control and the same daily dose was also effective in patients with arterial hypertension (Schütz *et al.*, 1982). Our preliminary findings with the 240 mg SR-verapamil tablets in the present group of hypertensive patients indicate that blood pressure lowering effects of a single dose persist up to

24 h. However, due to the considerable inter-individual variability of pharmacokinetics dosage of SR-verapamil has sometimes to be increased to 240 mg twice daily or 480 mg once daily to obtain serum concentrations above 50–100 ng ml⁻¹, which are often considered as the limit of therapeutic range. Whether once daily doses of SR-verapamil will also be possible in patients with arrhythmias, coronary artery disease and obstructive cardiomyopathy remains to be shown in controlled clinical trials.

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