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Chronic verapamil administration alters phenytoin pharmacokinetics in the rat

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Summary

The interaction of verapamil (4 and 8 mg/kg twice daily for 7 days) and i.v. phenytoin (10 mg/kg) in male Wistar rats has been studied. Increases occurred in phenytoin plasma elimination half-life (61%; $p < 0.01$ and 80%; $p < 0.05$), the area under the plasma concentration curve (32% n.s. and 48; $p < 0.05$) and volume of distribution (17%; $p < 0.05$ and 14% n.s.) after 4 and 8 mg/kg verapamil, respectively. The clearance was reduced to 75% (n.s.) and 67% ($p < 0.05$) of the control value; changes were not dose-dependent.

Verapamil is a calcium channel blocking agent used to treat angina, hypertension and cardiac arrhythmias as well as other clinical conditions (Kirkegaard et al., 1982; Rodheffer et al., 1983; Castell, 1985; Massey and Hendeles, 1987). It has been shown to inhibit microsomal drug metabolizing activity both in vivo and in vitro (Renton, 1985; Baur et al., 1986) and to alter the pharmacokinetic parameters of some drugs such as antipyrine and theophylline (Baur et al., 1986; Stringer et al., 1992) which undergo hepatic biotransformation.

The antiepileptic drug phenytoin is mainly used for grand mal epilepsy and is extensively metabolised by the liver. It has a dose-independent pharmacokinetic profile with a narrow therapeutic range; the adverse effects which tend to be concentration-dependent include drowsiness, dysarthia, tremor and ataxia (Atkinson and Shaw, 1973; Garrettson and Jusko, 1975; Laffey and Guzzardi, 1983; Bordie, 1990).

Both verapamil and phenytoin are required for long-term therapy. Some reports have highlighted the possibility of phenytoin altering verapamil pharmacokinetics (Woodcock et al., 1991). However, little attention has been focused on the possibility of verapamil altering phenytoin pharmacokinetics. In this report, the effects of verapamil on phenytoin pharmacokinetics have been investigated.

Adult male Wistar rats weighing 250–280 g were used. They were housed in an air-conditioned facility and fed standard pellet diet and

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water ad libitum. The animals were randomized into three groups: one received verapamil 4 mg/kg twice daily (ver. 4 group, $n = 6$), the second received verapamil 8 mg/kg twice daily (ver. 8 group, $n = 5$) and the third received an equivalent volume of water (control group, $n = 6$). Verapamil was obtained from Sigma Chemical Co. Phenytoin was used in the form of Epanutin 50 mg/ml injection (Park-Davis). All groups received the drug or water orally in a matched way for 7 days.

On the eighth day, a single dose of verapamil or water was administered to the animals, 1 h later phenytoin (10 mg/kg) was given intravenously via the femoral vein under light ether anaesthesia. Blood was taken with the aid of heparinised capillary tubes from tail tips. Samples (0.1 ml each) were collected before and at 5, 10, 20, 30, 45, 60, 90, 120, 180 and 240 min after phenytoin injection. The blood was centrifuged and plasma aliquots were separated for appropriate analysis.

Plasma phenytoin levels were determined by florescence polarization immunoassay using a Roche Cobas Fara II autoanalyser. In the range from 2.5 to 20 μg/ml the average coefficients of variation for this assay was 5.61 ($n = 3$).

Phenytoin plasma concentrations from individual animals were fitted by a computer programme for each rat by means of non linear regression analysis to a one-compartment pharmacokinetic model of the form:

$$C_t = Ae^{\alpha t}$$

where C_t is the concentration of the drug in the plasma at time t, A denotes the intercept and α is the elimination rate constant. Values obtained from these analyses were then used to calculate the elimination half-life ($t_{1/2}$), the area under the concentration curve ($AUC_{0-\infty}$), the volume of distribution (V_d) and the clearance (Cl) according to accepted formulae. A two-tailed Student's t-test was used to compare pharmacokinetic values between the three groups.

The pharmacokinetic values describing the disposition of phenytoin are listed in Table 1. These results indicate that the elimination half-life ($t_{1/2}$) and AUC of phenytoin were significantly higher in both treated groups when compared with the values obtained from the control group; V_d was also higher after 4 mg/kg ($p < 0.05$) and 8 mg/kg verapamil; Cl was lower in the treated groups than in the control group ($p < 0.05$, after 8 mg/kg verapamil).

In conclusion, the data obtained from the present study have demonstrated that phenytoin pharmacokinetic parameters of $t_{1/2}$, AUC and V_d increase significantly if phenytoin is administered concurrently with chronic administration of verapamil. The underlying mechanism behind the prolongation of phenytoin $t_{1/2}$ could have been due to an effect induced by verapamil on the liver enzymes. Phenytoin has been shown to be metabolised by the liver (Mays et al., 1987) and verapamil has been demonstrated to inhibit the activity of the liver drug metabolizing enzymes (Renton, 1985; Baur et al., 1986) which may indicate the possibility of reducing the rate of phenytoin metabolism. The observed increase in volume of distribution together with the associated increase in the elimination half-life can also be

TABLE 1

Phenytoin pharmacokinetic parameters in control and verapamil (4 and 8 mg / kg twice daily for 7 days) treated rats

	$t_{1/2}$ (min)	$AUC_{0-\infty}$ (μg ml^{-1} min)	V_d (l/kg)	Cl (ml kg^{-1} min^{-1})
Control ($n = 6$)	52.8 ± 8.0	891 ± 200	0.87 ± 0.15	11.7 ± 2.6
Ver. 4 ($n = 6$)	84.0 ± 21.3 [b]	1 184 ± 234 [a]	1.02 ± 0.10 [a]	8.89 ± 1.8
Ver. 8 ($n = 5$)	94.1 ± 45.2 [a]	1 318 ± 322 [a]	0.99 ± 0.22	7.9 ± 1.6 [a]

Values represent means ± SEM. [a] $p < 0.05$, [b] $p < 0.01$.

attributed to displacement of phenytoin from plasma proteins binding sites. Such an effect remains to be investigated.

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