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Verapamil disposition—effects of sulphinpyrazone and cimetidine

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1 The effects of separate 7 day pretreatments with sulphinpyrazone (800 mg daily) and cimetidine (1 g daily) on the disposition of (±)-verapamil have been examined in eight healthy volunteers (four male, four female).
2 Each subject received single oral (80 mg) and intravenous (0.15 mg/kg) doses of verapamil on different occasions before and after each pretreatment.
3 Following sulphinpyrazone pretreatment, verapamil apparent oral plasma clearance (CL_{po}) increased from 4.27 to 13.77 l h^{-1} kg^{-1} (s.e. mean 0.51—ANOVA) ($P < 0.001$); CL increased from 1.05 to 1.20 l h^{-1} kg^{-1} (s.e. mean 0.05) ($P < 0.05$) and F_{po} decreased from 27 to 10% administered dose (s.e. mean 2) ($P < 0.001$). V_{ss} and $t_{½,z}$ were unchanged.
4 There was no sex difference for any dispositional parameter in the control phase, but the increase in CL_{po} following sulphinpyrazone pretreatment was more marked in males (4.04 to 17.33 l h^{-1} kg^{-1}) than in females (4.49 to 10.21 l h^{-1} kg^{-1}) (s.e. mean 0.72) ($P < 0.01$).
5 There was no significant change in any verapamil disposition parameter following cimetidine pretreatment.
6 Verapamil unbound fraction in plasma was 0.157 (s.e. mean 0.001, $n = 40$). There was no alteration in verapamil plasma protein binding associated with increasing verapamil concentration (25–250 μg l^{-1}) or addition of sulphinpyrazone (50–500 mg l^{-1}) or cimetidine (0.5–5 mg l^{-1}).
7 The results suggest that sulphinpyrazone induces the metabolic clearance of (±)-verapamil with a sex difference in the response. This finding and the lack of effect of cimetidine pretreatment provide further evidence that a variety of isoenzymes catalyse drug oxidation in man and suggest a sex difference in its regulatory control.

Keywords verapamil sulphinpyrazone cimetidine drug disposition drug interaction

Introduction

The calcium channel antagonist verapamil, which is widely used in the treatment of angina, cardiac arrhythmias and arterial hypertension, is efficiently cleared from the body predominantly by hepatic metabolism. With hepatic extraction of greater than 70%, verapamil can be considered as a 'high clearance' drug which has systemic clearance limited by hepatic blood

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flow and a high presystemic clearance resulting in oral bioavailability less than 30% of the dose (Eichelbaum *et al.*, 1981; McAllister & Kirsten, 1982). Factors which alter the hepatic metabolic capacity for verapamil are thus likely to affect mainly the presystemic clearance and oral bioavailability of the drug (Wilkinson & Shand, 1975). As the major metabolic pathways for verapamil involve oxidative *N*-dealkylation (Eichelbaum *et al.*, 1979), drugs known to alter hepatic drug oxidation represent potential influences on verapamil metabolism and thus presystemic clearance. Two such agents are the histamine H_2-receptor antagonist, cimetidine, an inhibitor of the metabolic clearance of a number of drugs undergoing oxidation (Somogyi & Gugler, 1982), and the uricosuric and antiplatelet agent, sulphinpyrazone which has both inhibitory (Miners *et al.*, 1982) and inducing (Birkett *et al.*, 1983) effects on drug oxidation. The present study has investigated in the same healthy individuals the effect of pretreatment with sulphinpyrazone and with cimetidine on the disposition of verapamil following separate oral and intravenous doses. Possible sex differences in verapamil disposition and in the effects of the pretreatments were also examined.

Methods

Subjects

The subjects were eight healthy volunteers, four males (ages: 21–27 years, weight 58–85 kg) and four females (ages: 19–25 years, weight 56–72 kg) (Table 1). All were non-smokers. None of the females was taking hormonal contraceptives. All subjects had modest social ingestion of ethanol.

Prior to entry into the study, each subject underwent a comprehensive medical assessment including medical history, complete physical examination and screening haematology and biochemistry tests. None of the subjects had any history of chronic illness or any abnormality detected during the screening assessment. The study details were fully explained to each subject who was then asked to provide written consent to participation. The study was approved by the Clinical Investigation and Drug and Therapeutics Advisory Committees at Flinders Medical Centre.

Protocol

For each subject the study was conducted in three phases, a nonrandomised control phase was followed by two randomised phases, each of which involved a separate pretreatment period. The individual pretreatments were sulphinpyrazone orally 200 mg every 6 h and cimetidine orally 200 mg three times daily with meals and 400 mg at night prior to retiring. Each phase included 2 study days on which single doses of (±)-verapamil hydrochloride were administered in randomised order, an oral dose (80 mg) on 1 day and an intravenous (i.v.) dose (0.15 mg/kg administered by infusion pump over 10 min to a maximum of 10 mg) on the other day. There was a 1 day interval between the verapamil study days in each phase. The pretreatments were each commenced 7 days prior to the verapamil study days and continued until the 2 study days in the phase were complete. There was at least 1 week washout period between the two pretreatment phases.

Subjects fasted from 21.00 h on the evening prior to and until 4 h following verapamil administration on each study day. Dosing was at approximately 08.00 h on each occasion. During and for at least 20 min after the intravenous dose subjects rested supine, and in this period blood pressure was measured every 2 min and heart rate and electrocardiogram were monitored continually. Subjects then rested seated for a further hour prior to becoming freely mobile. Following the oral dose subjects were freely ambulant throughout.

On each study day a cannula was inserted into a forearm vein for subsequent blood sampling. The cannula was kept patent with heparinised saline (heparin 5 u/ml). On the intravenous study days a cannula was also inserted into a vein in the opposite forearm for drug administration. Venous blood samples (10 ml into a heparinised tube) were taken before dosing and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 24 and 28 h post-dosing on each occasion, and on the intravenous study days additional samples were also collected at the end of the infusion and at 10, 20 and 45 min post infusion. Plasma was separated and stored at −20°C prior to assay.

On one or more occasions several subjects noticed transient flushing and tachycardia during verapamil infusion and also symptoms such as headache and nausea at later times during the study days with both intravenous and oral verapamil. Three subjects reported these symptoms during the control phase and three subjects during the cimetidine pretreatment phase. Only one subject reported symptoms during the sulphinpyrazone phase, headache in the first hour post-infusion.

Analytical methods

All drug concentrations were measured by high performance liquid chromatography. Verapamil concentrations were measured by the method of Harapat & Kates (1980); sulphinpyrazone concentrations were measured by a modification of the procedure described by Wong *et al.* (1978) using phenprocoumon as the internal standard; and cimetidine concentrations were measured by a method previously described from our laboratory (Wing *et al.*, 1984).

Verapamil plasma protein binding was measured after dialysis of pooled normal plasma for 3 h at 37°C to equilibrium against phosphate buffer pH 7.4 containing unlabelled verapamil and trace amounts of [^{14}C]-verapamil.

Parameters of verapamil disposition

For each subject on each verapamil study day the following parameters were calculated from the verapamil plasma concentration-time data: AUC by the trapezoidal rule with extrapolation to infinity assuming first order kinetics; $t_{42,z}$ from the slope of the terminal portion of the curve by linear least squares regression; V_{ss} by a model-independent method (Benet & Galeazzi, 1979); systemic clearance (CL) as $D_{iv}/(AUC_{iv} \times$ body weight); apparent oral clearance (CL_{po}) as $D_{po}/(AUC_{po} \times$ body weight); and F_{po} as $(CL/CL_{po}) \times 100$ and expressed as a percentage of the oral dose.

Statistical analysis

For each parameter, group values are expressed as mean ± s.e. mean (calculated either directly or from the respective ANOVA residual mean square). A mixed design ANOVA was employed to compare differences between phases (within subjects) and between sexes and randomisation groups (between subjects) (Winer, 1971).

For the sulphinpyrazone and cimetidine plasma concentrations on the separate study days in the respective pretreatment phases, AUC in the interval predose to 6 h was calculated. Group values are expressed as average plasma concentration (mean ± s.e. mean) for the separate oral and intravenous study days. Differences between these group mean values for each pretreatment were examined using a paired *t*-test.

Results

Representative plasma concentration-time data for one subject (GK) are shown in Figure 1. In each subject there was little difference in the AUCs following the intravenous doses of verapamil on the three different occasions. In contrast, with the oral doses of verapamil the AUC following sulphinpyrazone pretreatment was markedly reduced compared to the AUCs in the control phase and following cimetidine pretreatment. The calculated dispositional parameters for each subject, males, females and the whole group are shown in Table 1.

Sulphinpyrazone pretreatment

Following sulphinpyrazone pretreatment all subjects showed an increase in CL_{po} compared with the control phase, the mean increase being from 4.27 to 13.77 l h^{-1} kg^{-1} ($P < 0.001$) (Table 1). Although CL_{po} was similar in both sexes in the control phase, the increase in CL_{po} following sulphinpyrazone was more marked in males (4.04 to 17.33 l h^{-1} kg^{-1}) than in females (4.49 to 10.21 l h^{-1} kg^{-1}) ($P < 0.01$) (Table 1). There was a small increase in mean CL from 1.05 to 1.20 l h^{-1} kg^{-1} ($P < 0.05$) although individual responses were inconsistent. F_{po} was reduced in all subjects, from 27 to 10% ($P < 0.001$). No significant changes were observed in verapamil V_{ss} or $t_{42,z}$. There were no significant sex differences for any parameter in the control phase or, other than for CL_{po}, following sulphinpyrazone. There was no difference in sulphinpyrazone average plasma concentration on the two study days in the sulphinpyrazone phase (Table 2).

Cimetidine pretreatment

There was no significant change for the group as a whole or in either sex in any verapamil disposition parameter following cimetidine pretreatment (Table 1). Similarly, there was no difference in the cimetidine AUC on the two study days in the cimetidine phase (Table 2). The effects of sulphinpyrazone and cimetidine were not affected by order of administration.

Verapamil protein binding

Verapamil unbound fraction was 0.157 ± 0.001 ($n = 40$). There was no alteration in verapamil plasma protein binding associated with increasing verapamil concentration (25–250 μg l^{-1}) or addition of sulphinpyrazone (50–500 mg l^{-1}) or cimetidine (0.5–5 mg l^{-1}).

Discussion

Sulphinpyrazone has been shown to have differential effects on at least two forms of cytochrome

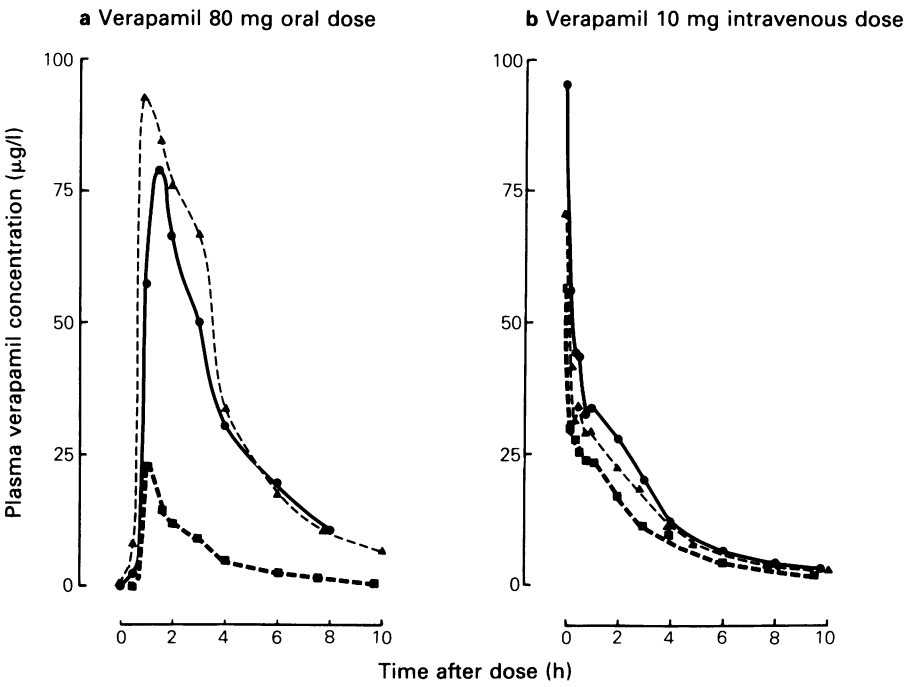

Figure 1 Representative verapamil plasma concentration-time data for one subject (GK). • control, ▲ after cimetidine, ■ after sulphinpyrazone.

P-450 in man and is known both to inhibit (Miners *et al.*, 1982) and to induce (Birkett *et al.*, 1983) oxidative drug metabolism. In the present study the increase in verapamil CL_{po} following sulphinpyrazone pretreatment is thus consistent with induction of the presystemic metabolism of verapamil. Although the metabolism of verapamil is complex the predominant pathways are *N*-dealkylation and *N*-demethylation (Eichelbaum *et al.*, 1979) suggesting that it is these oxidative pathways which are induced by sulphinpyrazone.

Other possible explanations of the alteration in verapamil CL_{po} following sulphinpyrazone pretreatment are changes in verapamil plasma protein binding or gastrointestinal absorption. *In vitro* data do not support any effect of sulphinpyrazone on verapamil plasma protein binding. In addition the observed *in vivo* dispositional data make it highly unlikely that there was an effect of sulphinpyrazine on verapamil plasma protein binding, as an increase in V_{ss} would also have been expected (Wilkinson & Shand, 1975) but there was no change in V_{ss}. Although urinary recovery measurements have not been made in this study, there is no previous evidence to implicate sulphinpyrazone in the reduction of the gastrointestinal absorption of other drugs.

The clinical significance of this interaction between sulphinpyrazone and verapamil is presently unclear. As verapamil is a racemic mixture, the two enantiomers of which have different pharmacological activities (Kaumann & Serur, 1975; Saikawa & Arita, 1980; Satoh *et al.*, 1980) and probably different dispositions (Eichelbaum *et al.*, 1980), alterations in the disposition of racemic verapamil cannot necessarily be equated with net changes in pharmacological response, which was not specifically measured in the present study. As the observed increase in CL_{po} was large, particularly in the male subjects, it is probable that CL_{po} of both enantiomers has been affected with consequent net reduction in the oral bioavailability of active drug. The significance of the small increase in CL following sulphinpyrazone is unclear, as this was not a consistent change in contrast to the increase in CL_{po}. Further studies are in progress to elucidate the effect of this dispositional interaction on the pharmacological response to verapamil.

Although sex differences in oxidative drug metabolism are well known in the rat (Kato, 1974), only recently have such differences been demonstrated in humans (Allen *et al.*, 1980; Greenblatt *et al.*, 1980; Roberts *et al.*, 1979; Teunissen *et al.*, 1982). This study has shown an

Table 1 Verapamil disposition in control phase and following sulphinpyrazone and cimetidine pretreatments

			CL_{po} ($l\ h^{-1}\ kg^{-1}$)			CL ($l\ h^{-1}\ kg^{-1}$)			F_{po} (% dose)			V_{ss} ($l\ kg^{-1}$)			$t_{½,z}$ (h) (i.v. dose)		
	Age (years)	*Weight (kg)*	*Control*	*SPZ**	*CIM†*	*Control*	*SPZ*	*CIM*	*Control*	*SPZ*	*CIM*	*Control*	*SPZ*	*CIM*	*Control*	*SPZ*	*CIM*
Males (n = 4)																	
NM	26	85.0	3.55	13.21	2.99	0.92	0.75	0.86	26	6	29	2.67	1.14	2.64	2.3	2.1	1.4
RS	21	58.5	2.60	15.86	3.93	1.22	1.15	1.01	47	7	26	3.66	3.47	3.15	2.0	2.0	1.1
GK	21	70.0	3.97	18.98	3.20	0.78	1.20	0.88	20	6	28	2.71	4.34	3.46	2.6	2.8	2.7
NR	27	72.1	6.05	21.26	5.66	0.91	1.14	0.99	15	5	18	3.68	4.50	4.27	2.8	3.0	2.8
Mean	23.8	71.4	4.04	17.33	3.95	0.96	1.06	0.94	27	6	25	3.18	3.36	3.38	2.4	2.5	2.0
s.e. mean	1.6	5.4		0.72			0.07			3			0.35			0.1	
Females (n = 4)																	
MA	21	56.0	3.51	10.93	3.23	0.89	1.40	0.89	25	13	27	2.43	4.03	2.64	2.2	2.2	2.6
PD	25	72.7	3.85	10.16	4.78	1.30	1.26	0.98	34	12	21	4.57	3.30	3.26	2.6	2.5	2.5
MC	21	57.3	6.14	8.73	5.15	1.37	1.34	1.24	22	15	24	5.38	4.26	3.67	2.6	2.1	2.4
KJ	19	57.5	4.46	11.00	2.95	1.02	1.38	0.97	23	13	33	2.89	3.36	2.03	2.1	1.7	2.0
Mean	21.5	60.9	4.49	10.21	4.03	1.15	1.35	1.02	26	13	26	3.82	3.74	2.90	2.4	2.2	2.3
s.e. mean	1.3	4.0		0.72			0.07			3			0.35			0.1	
Group (n = 8)																	
Mean	22.7	66.1	4.27	13.77	3.99	1.05	1.20	0.98	27	10	26	3.50	3.55	3.14	2.4	2.3	2.2
s.e. mean	1.0	3.7		0.51			0.05			2			0.25			0.1	
Difference from control P				<0.001	NS‡		<0.05	NS		<0.001	NS		NS	NS		NS	NS

* SPZ = sulphinpyrazone pretreatment phase
† CIM = cimetidine pretreatment phase
‡ NS = non-significant ($P > 0.05$)

Table 2 Sulphinpyrazone and cimetidine average plasma concentrations in the interval pre-dose to 6 h post-dose

	Verapamil oral dose study	*Verapamil intravenous dose study*
Sulphinpyrazone	9.0 ± (1.0)	9.8 ± (1.1)
Cimetidine	0.7 ± (0.1)	0.8 ± (0.1)

Values in mg l^{-1} are group means (s.e. mean), $n = 8$

apparent sex difference in the extent of induction of verapamil metabolism by sulphinpyrazone suggesting possible sex differences in the regulatory control of oxidative drug metabolism. Failure to observe such sex differences in drug metabolism more commonly in humans may relate more to the choice of subjects (usually only healthy males are used) and to the dispositional parameters measured.

As cimetidine has now been shown to inhibit the oxidative metabolism of a wide range of drugs (Somogyi & Gugler, 1982), failure to observe any effect of cimetidine pretreatment on verapamil disposition was relatively unexpected. Although differential effects of cimetidine on the disposition of the verapamil enantiomers could have masked net changes for racemic verapamil, this is unlikely as it would require that cimetidine should induce the CL_{po} of at least one enantiomer—this would be a unique finding. More detailed study of the effects of cimetidine on the individual oxidative pathways of theophylline has revealed that while cimetidine inhibits 1- and 3-demethylation the 8-oxidation was not significantly affected (Birkett *et al.*, 1981), suggesting that cimetidine does not inhibit all forms of cytochrome P-450 to an equal extent. The finding in the present study would thus appear to be a further example of cimetidine not inhibiting a particular oxidative pathway. Both this lack of effect of cimetidine and the presumed observed induction of verapamil oxidation by sulphinpyrazone provide further evidence in man for a variety of isoenzymes being involved in drug oxidation. The results of this study demonstrate that our present state of knowledge clearly does not allow us to be able to predict metabolic interactions between particular drug combinations.

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