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Selective inhibitory effects of nifedipine and verapamil on oxidative metabolism: effects on theophylline

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Nine healthy male volunteers were studied to assess the possibility of an interaction between theophylline and nifedipine or verapamil using a randomised, crossover design. Subjects received theophylline 125 mg 8 hourly with and without nifedipine 20 mg 12 hourly and verapamil 80 mg 8 hourly. Nifedipine treatment reduced mean total theophylline clearance by 9%, due to decreased clearances via 1- and 3-demethylation. Verapamil treatment reduced mean total theophylline clearance by 14%, due to decreased clearances via 1- and 3-demethylation and 8-hydroxylation. Verapamil and nifedipine at usual clinical doses are unlikely to cause clinically significant changes in theophylline disposition.

Keywords theophylline nifedipine verapamil interaction cytochrome P-450

Introduction

The calcium channel blockers verapamil and nifedipine are commonly used in combination with theophylline for the treatment of angina and hypertension in asthmatic patients. *In vitro* studies of theophylline metabolism in human liver microsomes demonstrated that the calcium channel blockers nifedipine and verapamil both inhibited theophylline metabolism (Robson *et al.*, 1988). Verapamil inhibited the 1- and 3-demethylation and the 8-hydroxylation pathways of theophylline metabolism to a similar extent. Nifedipine inhibited the demethylation pathways to a greater extent than the 8-hydroxylation pathway.

Verapamil has been demonstrated to inhibit the clearances of antipyrine (Bauer *et al.*, 1986; Rumiantsev *et al.*, 1986) and carbamazepine (Macphee *et al.*, 1986) in man. A case report suggests that verapamil may also inhibit theophylline clearance (Burnakis *et al.*, 1983). Consistent with this observation is the fact that sulphinpyrazone pretreatment induces the metabolic clearances of both theophylline and verapamil (Birkett *et al.*, 1983; Wing *et al.*, 1985) suggesting that the same (or similarly regulated) isozyme(s) of cytochrome P-450 may be involved in the metabolism of both theophylline and verapamil. Antipyrine metabolic clearance is reduced by verapamil but not nifedipine treatment (Bauer *et al.*, 1986). Nifedipine has recently been shown not to alter the pharmacokinetic or pharmacodynamic parameters of theophylline in asthmatic patients (Garty *et al.*, 1986), although the effects on individual theophylline metabolic pathways were not investigated. It is possible that nifedipine may selectively affect individual theophylline metabolic clearances *in vivo* without substantially changing total clearance. This study was therefore undertaken to assess possible effects of treatment with clinical doses of verapamil and nifedipine on the individual metabolic pathways of theophylline in a group of healthy volunteers.

Methods

The subjects were nine non-smoking male volunteers aged (mean ± s.d.) 21.3 ± 3.5 (range 18–30) years and weighing 70.4 ± 7.2 (range 58–80) kg who were healthy as determined by medical history, physical examination and standard biochemical and haematological parameters. Subjects abstained from methylxanthine containing foods and beverages for 3 days prior to and during each study phase. No medications, other than those required for the study, were taken for 1 week prior to and during each study phase. A randomised three way crossover study design was used with a 2 week washout period

between each phase. The study details were fully explained to each subject who then gave written consent to participate. The studies were approved by the Clinical Investigation and Drug and Therapeutics Advisory Committees at Flinders Medical Centre.

Subjects received theophylline (Nuelin-Riker) 125 mg orally 8 hourly for 4 days in the control phase. In the nifedipine phase, subjects received nifedipine (Adalat-Bayer) 20 mg tablets orally 12 hourly in addition to the theophylline for 4 days. In the verapamil phase subjects received verapamil (Isoptin-Knoll) 80 mg orally 8 hourly in addition to the theophylline for 4 days. On day 4 of each phase, venous blood samples (5 ml) were collected through an indwelling intravenous catheter prior to and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7 and 8 h after the morning dose. On each study day, the dose of verapamil or nifedipine was administered at the same time as the theophylline. Total urine was collected over the same 8 h dosing interval in each phase. Plasma was separated and stored at -20° C until analysed and urine was diluted 1:1 with 0.1 M acetic acid and kept at -20° C until analysed.

Analytical procedures

Theophylline plasma concentrations were determined using the Abbott TDX fluorescence polarisation immunoassay. Concentrations of unchanged theophylline and theophylline metabolites (3-methylxanthine [3MX], 1-methyluric acid [1MU], and 1,3-dimethyluric acid [1,3DMU] in urine were measured using high performance liquid chromatography (Birkett *et al.*, 1985). In all assays the intra-assay coefficients of variation were less than 7%.

Analysis of results

Area under the theophylline plasma concentration time curve over the dose interval (AUC) was calculated by the trapezoidal rule and total plasma theophylline clearance (CL) as:

$$CL = Dose/(AUC \times BW)$$

where BW is body weight in kg. Partial metabolic and renal clearances of theophylline were calculated as:

$$CL_i = f_i \times CL$$

where CL_i is the metabolic clearance to 1MU (CL_{1MU}), 3MX (CL_{3MX}) or 1,3DMU (CL_{DMU}) or the renal clearance of unchanged theophylline (CL_R), and f_i is the fractional urinary recovery of each metabolite as a fraction of the total recovery of theophylline and metabolites.

Results are expressed as mean ± s.d. The significance of the differences between study phases for both studies was determined by analysis of variance. Individual comparisons were performed using Student's paired *t*-test.

Results

The effects of pretreatment with nifedipine and verapamil on theophylline total plasma clearance (CL) and on the renal and metabolic clearances of theophylline are summarised in Table 1.

Verapamil reduced theophylline CL by 14%, from 0.682 ± 0.102 to 0.589 ± 0.113 ml min^{-1} kg^{-1} ($P = 0.01$). The reduction in CL was due to a 15% decrease in CL_{DMU} from 0.341 ± 0.054 to 0.289 ± 0.061 ml min^{-1} kg^{-1} ($P = 0.03$); a 20% reduction in CL_{1MU}, from 0.156 ± 0.031 to 0.125 ± 0.037 ml min^{-1} kg^{-1} ($P = 0.03$) and a 10% reduction in CL_{3MX}, from 0.117 ± 0.032 to 0.106 ± 0.033 ml min^{-1} kg^{-1} ($P = 0.06$). Renal clearance of unchanged theophylline was not significantly altered by verapamil pretreatment ($P > 0.1$). The individual data are shown in Table 1.

Nifedipine reduced theophylline CL by 9% from 0.682 ± 0.102 to 0.618 ± 0.102 ml min^{-1} kg^{-1} ($P = 0.01$). The decrease in CL was due to a 15% decrease in CL_{1MU}, from 0.156 ± 0.031 to 0.133 ± 0.03 ml min^{-1} kg^{-1} ($P = 0.01$) and a 10% decrease in CL_{3MX}, from 0.117 ± 0.032 to 0.105 ± 0.021 ml min^{-1} kg^{-1} ($P = 0.06$). CL_{DMU} and CL_R were not significantly altered ($P > 0.1$). Individual data are shown in Table 1.

The recoveries of theophylline derived urinary products were not statistically different in each phase, being 94 ± 10%, 99 ± 7% and 90 ± 6% in the control, verapamil and nifedipine phases, respectively. The attainment of steady state on the 3 study days was confirmed by trough concentrations within 10% at the beginning and end of the dosage intervals. The study design was sufficiently sensitive to detect a 6–8% change in the measured parameters for theophylline with an α value of 0.05 and a β value of 0.2.

Discussion

Verapamil treatment reduced mean plasma theophylline clearance by 14% due to reductions in all three theophylline metabolic clearances. The magnitude of the reduction in clearance was

Table 1 Effect of verapamil and nifedipine on metabolic and renal clearance of theophylline

Subject	T^2	CL_P* *TV*	*TN*	*T*	CL_{DMU} *TV*	*TN*	*T*	CL_{1MU} *TV*	*TN*	*T*	CL_{3MX} *TV*	*TN*	*T*	CL_R *TV*	*TN*
1	0.595	0.457	0.631	0.267	0.199	0.306	0.148	0.081	0.144	0.080	0.061	0.092	0.101	0.116	0.089
2	0.740	0.670	0.569	0.381	0.353	0.274	0.129	0.105	0.125	0.117	0.117	0.101	0.056	0.096	0.069
3	0.674	0.549	0.604	0.352	0.276	0.329	0.153	0.121	0.124	0.119	0.097	0.095	0.051	0.055	0.057
4	0.666	0.551	0.571	0.332	0.272	0.272	0.156	0.130	0.136	0.101	0.118	0.094	0.076	0.031	0.070
5	0.525	0.462	0.427	0.253	0.226	0.208	0.131	0.103	0.084	0.077	0.062	0.072	0.064	0.071	0.064
6	0.800	0.614	0.621	0.368	0.265	0.276	0.210	0.143	0.141	0.168	0.148	0.143	0.055	0.058	0.061
7	0.600	0.507	0.620	0.350	0.278	0.356	0.113	0.087	0.113	0.100	0.088	0.100	0.038	0.054	0.051
8	0.695	0.731	0.785	0.338	0.376	0.421	0.172	0.193	0.195	0.128	0.113	0.121	0.057	0.049	0.047
9	0.847	0.765	0.738	0.430	0.358	0.434	0.193	0.166	0.139	0.163	0.153	0.125	0.062	0.088	0.040
Mean	0.682	0.589	0.618	0.341	0.289	0.320	0.156	0.125	0.133	0.117	0.106	0.105	0.062	0.069	0.061
s.d.	0.102	0.113	0.102	0.054	0.061	0.074	0.031	0.037	0.030	0.032	0.033	0.021	0.018	0.027	0.015
P		0.01	0.01		0.03	NS		0.01	0.01		0.06	0.06		NS	NS

* Units of clearance are ml min^{-1} kg^{-1}.

[2]T, theophylline alone; TV, theophylline plus verapamil; TN, theophylline plus nifedipine.

small and of only marginal significance for 3MX formation. This contrasts with the case report (Burnakis *et al.*, 1983) which reported a 100% increase in plasma theophylline concentration during verapamil treatment. The non-selective, weak inhibitory effect of verapamil pretreatment on the disposition of theophylline is consistent with our *in vitro* data. The present data suggests that verapamil does not interact with theophylline to a clinically important extent.

Nifedipine treatment had only minor effects on theophylline metabolism *in vivo*. Mean plasma clearance was reduced by 9% due to 15% and 10% reductions in partial metabolic clearances to 1MU and 3MX, respectively. Although small, these changes were statistically significant due to the power of the study. The present data are consistent with previous reports which found no change in theophylline disposition with nifedipine treatment of asthmatic subjects (Jackson *et al.*, 1986; Garty *et al.*, 1986). Further, our study shows that nifedipine has little effect on the individual pathways for theophylline metabolism. Recent *in vitro* studies by us with human liver microsomes found that nifedipine was an inhibitor of theophylline 1- and 3-demethylations, but not of 8-oxidation (Robson *et al.*, 1988). While the effect of nifedipine *in vivo* was least marked on the 8-oxidation pathway the overall degree of inhibition was small, presumably due to the low nifedipine concentrations (compared with those used *in vitro*) achieved in the liver with usual clinical doses. The present study shows that nifedipine and verapamil at usual clinical doses are unlikely to cause clinically significant changes in theophylline disposition.

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