Specificity of the inhibitory effect of dextropropoxyphene on oxidative drug metabolism in man: effects on theophylline and tolbutamide disposition

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Two groups of six healthy male volunteers were studied to assess the possibility of an interaction between dextropropoxyphene and theophylline or tolbutamide using a randomised, crossover design. Subjects received theophylline 125 mg 8 hourly or tolbutamide 500 mg i.v. with and without dextropropoxyphene hydrochloride 65 mg 8 hourly. Theophylline 8-hydroxylation was reduced by a mean of 17% but there were no changes in theophylline 1-demethylation, theophylline 3-demethylation or tolbutamide hydroxylation.

Keywords dextropropoxyphene tolbutamide theophylline metabolism cytochrome P-450

Introduction

Dextropropoxyphene inhibits the cytochrome P-450 dependent metabolism of carbamazepine, phenobarbitone, phenytoin and alprazolam in man (Hansen *et al.*, 1980; Dam & Christiansen, 1977; Abernethy *et al.*, 1985). Dextropropoxyphene may be a general inhibitor of the cytochrome P-450 system in man, or a selective inhibitor of only some isozymes.

We have previously suggested that at least two isozymes of cytochrome P-450 are involved in the metabolism of theophylline, one isozyme being involved with the two *N*-demethylations and the other isozyme involved with the C8-oxidation (Birkett *et al.*, 1985). The isozymes involved with theophylline are clearly different from the isozyme involved in tolbutamide hydroxylation as sulphinpyrazone inhibits tolbutamide hydroxylation (Miners *et al.*, 1982) but induces theophylline metabolism (Birkett *et al.*, 1983), cimetidine inhibits theophylline metabolism (Grygiel *et al.*, 1984) but does not inhibit tolbutamide (Dey *et al.*, 1983) and cigarette smoking induces theophylline metabolism (Grygiel & Birkett, 1981) but has no effect on tolbutamide metabolism (Scott & Poffenbarger, 1979). The present study was designed to establish if dextropropoxyphene selectively inhibited

the isozymes involved in the metabolism of theophylline and tolbutamide. In addition, theophylline and tolbutamide are drugs with narrow therapeutic indices and inhibition of the metabolism of either drug by dextropropoxyphene may cause a clinically significant interaction.

Methods

The subjects were twelve non-smoking male volunteers who were healthy as determined by medical history, physical examination and standard biochemical and haematological parameters. Six subjects (mean $\pm$ s.d. age 20.5 ± 4.4 years, weight 82.0 ± 27 kg) participated in the theophylline study and six subjects (age 20.7 ± 6.1 years, weight 74.9 ± 10.4 kg) participated in the tolbutamide study. The six subjects involved in the theophylline study abstained from methylxanthine containing foods and beverages for 3 days prior to and during the study. A randomised crossover study design was used for both studies with a 3 week washout period between each phase. No other medications were taken for 2 weeks prior to or during the study. The details of each study 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.

For the theophylline study, the six subjects received theophylline (Nuclin tablet, Riker) 125 mg orally 8 hourly for 4 days in one phase and theophylline 125 mg and dextropropoxyphene HCl 65 mg orally every 8 h in the other phase. On the fourth day of each phase, venous plasma samples (5 ml) were collected through an indwelling cannula inserted in a forearm vein prior to and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6 and 8 h after the morning dose. Total urine was collected over the 8 h dosage interval. Plasma was separated and stored at -20°C until assayed and the urine was diluted 1:1 with 0.1 M acetic acid and stored at -20°C until analysed.

For the tolbutamide study, the six subjects received, after an overnight fast, 500 mg tolbutamide (Rastinon, Hoechst) as a constant infusion 50 mg min^{-1} into an infusion (10 ml min^{-1}) of normal saline via an indwelling intravenous cannula. Venous blood samples (5 ml) were collected through an indwelling cannula inserted into a forearm vein in the opposite arm to the infusion site prior to and at 5, 10, 15, 30, 45 min and 1, 2, 4, 6, 7, 24, 28 and 32 h after the start of the infusion. Blood glucose was measured at 0, 0.5, 1.0, 2.0 and 4.0 h after the tolbutamide infusions. Intravenous 5% dextrose and oral glucose was available to treat any significant hypoglycaemia. In the dextropropoxyphene phase the subjects received dextropropoxyphene HCl 65 mg orally 8 hourly for 5 days. On the 4th day the subjects were administered the infusion of tolbutamide at the time of the morning dose of dextropropoxyphene using the same protocol as detailed above. Plasma was separated and stored 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%.

Tolbutamide plasma concentrations were determined by a specific high performance liquid chromatographic procedure (Miners *et al.*, 1982). Tolbutamide plasma protein binding was measured by equilibrium dialysis using [^{14}C]-

tolbutamide as previously described (Miners *et al.*, 1982).

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 $\text{CL} = \text{Dose}/(\text{AUC} \times \text{BW})$, where BW in body weight in kg. Partial metabolic and renal clearances of theophylline were calculated as $\text{CL}_i = f_i \times \text{CL}$, where CL_i is the metabolic clearance to 1MU ($\text{CL}_{1\text{MU}}$), 3MX ($\text{CL}_{3\text{MX}}$) 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.

From the tolbutamide plasma concentration-time curve data the apparent elimination rate constant (k_e) was calculated by linear least-squares regression analysis using the data points from 2 to 32 h after the infusion. Area under the plasma concentration-time curve was calculated by the trapezoidal rule with extrapolation to infinite time by C_{last}/k_e .

Plasma tolbutamide clearance was calculated from: $\text{CL} = \text{Dose}/\text{AUC}_{\infty}^{\infty}$. Half-life ($t_{1/2}$) was calculated as $0.693/k_e$ and volume of distribution by a model independent method (Benet & Galeazzi, 1979). The significance of the differences between study phases for both studies was determined using Wilcoxon matched-pairs signed-ranks test. The null hypothesis was rejected when $P \leq 0.05$.

Results

The effects of dextropropoxyphene on theophylline plasma clearance (CL) and on the renal and metabolic clearances of theophylline are summarised in Table 1.

Theophylline plasma CL was $0.65 \pm 0.016\text{ ml min}^{-1}\text{ kg}^{-1}$ in the control phase and $0.58 \pm 0.014\text{ ml min}^{-1}\text{ kg}^{-1}$ with dextropropoxyphene treatment, but this change was not statistically significant ($P = 0.17$). CL_{DMU} decreased from 0.33 ± 0.08 to $0.27 \pm 0.06\text{ ml min}^{-1}\text{ kg}^{-1}$ ($P = 0.03$) but $\text{CL}_{1\text{MU}}$, $\text{CL}_{3\text{MX}}$ and CL_R were not significantly altered by dextropropoxyphene pretreatment ($P > 0.05$). Recoveries of theophylline derived products in the urine were $84 \pm 1.2\%$ in the control phase and $86 \pm 1.6\%$ in the dextropropoxyphene phase. The attainment of steady state on the two study days was confirmed by theophylline trough concentrations within $\pm 10\%$ at the beginning and end of the dosage interval on each study day.

Table 1 Effect of dextropropoxyphene on metabolic and renal clearances of theophylline

Subject	CL ¹		CL _{1MU}		CL _{3MX}		CL _{DMU}		CL _R	
	T ²	TD	T	TD	T	TD	T	TD	T	TD
1	0.760	0.665	0.236	0.193	0.123	0.096	0.366	0.317	0.040	0.058
2	0.528	0.548	0.141	0.151	0.077	0.093	0.280	0.265	0.032	0.034
3	0.498	0.388	0.148	0.113	0.061	0.050	0.259	0.202	0.030	0.022
4	0.727	0.762	0.203	0.241	0.104	0.128	0.351	0.318	0.044	0.075
5	0.501	0.469	0.120	0.098	0.053	0.065	0.254	0.212	0.075	0.095
6	0.887	0.669	0.207	0.168	0.120	0.105	0.459	0.325	0.066	0.070
Mean	0.650	0.584	0.176	0.161	0.090	0.089	0.328	0.273	0.048	0.059
95% confidence limits	± 0.168	± 0.147	± 0.053	± 0.053	± 0.032	± 0.032	± 0.084	± 0.063	± 0.021	± 0.032
s.d. mean	0.16	0.14	0.05	0.05	0.03	0.03	0.08	0.06	0.02	0.03
P	0.17		0.25		0.92		0.03		0.12	

¹ Units of clearance are ml min⁻¹ kg⁻¹.
² T, theophylline alone; TD, theophylline plus dextropropoxyphene.

Table 2 Effect of dextropropoxyphene on tolbutamide pharmacokinetic parameters

Subject	Half-life (h)		Clearance (ml min ⁻¹ kg ⁻¹)		Volume of distribution (l kg ⁻¹)	
	T	TD	T	TD	T	TD
1	5.42	7.28	0.30	0.31	0.11	0.17
2	7.02	6.32	0.23	0.24	0.13	0.12
3	7.59	7.32	0.22	0.19	0.12	0.11
4	4.66	5.13	0.23	0.22	0.09	0.08
5	6.75	6.45	0.20	0.18	0.06	0.09
6	5.94	7.08	0.22	0.17	0.10	0.09
Mean	6.23	6.60	0.24	0.22	0.10	0.11
95% confidence limits	± 1.14	± 0.84	± 0.042	± 0.053	± 0.021	± 0.032
s.d.	1.09	0.8	0.04	0.05	0.02	0.03
	NS		NS		NS	

T tolbutamide alone, TD tolbutamide plus dextropropoxyphene.

The effects of dextropropoxyphene pretreatment on tolbutamide CL, volume of distribution and half-life are summarised in Table 2. No subject developed any significant hypoglycaemia after the tolbutamide infusions. Tolbutamide protein binding was not affected by dextropropoxyphene treatment with the same free fraction in both phases over the plasma tolbutamide concentration range. There were no statistically significant effects of dextropropoxyphene on any of the measured tolbutamide disposition parameters.

The study designs were sufficiently sensitive to detect 10% changes in the measured parameters for theophylline and tolbutamide with an α value of 0.05 and a β value of 0.2.

Discussion

Pretreatment with dextropropoxyphene did not significantly alter theophylline plasma CL. There was a small (17%), statistically significant decrease in CL_{DMU} but the demethylation clearances were not significantly changed. This may suggest a selective effect of dextropropoxyphene on the 8-hydroxylation pathway. Previous studies have shown that dextropropoxyphene decreases the clearance of carbamazepine by 40% to 61% (Hansen *et al.*, 1980; Dam & Christiansen, 1977),

and alprazolam clearance by 38.5% (Abernethy *et al.*, 1985). Smaller reductions in clearance have been observed with phenytoin (14%) and phenobarbitone (20%) by Hansen *et al.* (1980) and with diazepam (13%) by Abernethy *et al.* (1985). In the present study there was a 17% decrease in theophylline 8-hydroxylation and no significant changes in theophylline 1- and 3-demethylations or tolbutamide hydroxylation. Overall these data suggest that dextropropoxyphene is not a general inhibitor of oxidative drug metabolism in man but selectively inhibits only some isozymes of cytochrome P-450. It is therefore not possible to predict whether any individual drug substrate will be affected by dextropropoxyphene. Separate studies will be required in each case.

For drugs with narrow therapeutic indices it is important to determine the possibility of interactions with dextropropoxyphene because of its extensive use in compound analgesics. The present study demonstrates that there is no clinically important interaction between dextropropoxyphene and theophylline or tolbutamide.

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