Br. J. clin. Pharmac. (1984), **18**, 445–448

Theophylline-rifampicin interaction: non-selective induction of theophylline metabolic pathways

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The effect of rifampicin pre-treatment (600 mg daily for 6 days) on theophylline disposition at steady state was investigated in six healthy males. Following rifampicin treatment total plasma clearance of theophylline increased by 82%. Theophylline clearance through each metabolic pathway was increased, 1-demethylation by (116 ± 34%) (mean ± s.e. mean), 3-demethylation by (91 ± 16%) and 8-oxidation by (81 ± 17%). Renal clearance of unchanged drug was not altered. Previous studies have suggested that two forms of cytochrome P-450 are involved in theophylline metabolism, one mediating the *N*-demethylations and the other 8-oxidation. Thus, unlike the selective inductive effect of rifampicin on antipyrine metabolic pathways, rifampicin does not differentially affect those forms of cytochrome P-450 involved in theophylline metabolism. The extent to which theophylline metabolism is induced by rifampicin is likely to have important clinical consequences.

Keywords theophylline rifampicin drug metabolism induction interaction

Introduction

Rifampicin is considered to be an inducer of the hepatic mixed function oxidase system in man because it is known to enhance the elimination of a number of drugs primarily cleared by metabolic oxidation—antipyrine (Toverud *et al.*, 1981), hexobarbitone (Zilly *et al.*, 1975), oral contraceptive steroids (Nocke-Finck *et al.*, 1973), tolbutamide (Zilly *et al.*, 1975) and warfarin (O'Reilly, 1974).

More recently, rifampicin pretreatment was reported to increase theophylline clearance in normal volunteers (Hauser *et al.*, 1983), although effects on the specific metabolic pathways of theophylline were not determined. Theophylline (1,3-dimethylxanthine) is metabolised by cytochrome P-450 by demethylations in the 1- and 3-positions to 3-methylxanthine (3MX) and 1-methylxanthine (1MX) respectively, and by 8-oxidation to 1,3-dimethyluric acid (1,3DMU) (Birkett *et al.*, 1983a; Grygiel *et al.*, 1979). Once formed, 1MX is converted to 1-methyluric acid (1MU) by xanthine oxidase. There is evidence to suggest that the two demethylations may be under different regulatory control to the 8-oxidation (Birkett *et al.*, 1982; Grygiel & Birkett, 1981). Thus, to define further the effects of rifampicin on oxidative drug metabolism in healthy subjects under steady-state dosing conditions, this study determines the effect of rifampicin pretreatment on the partial metabolic clearance to the individual metabolites and the renal clearance of unchanged theophylline.

Methods

Protocol

The subjects were six non-smoking male volunteers (age 20–45 years, weight 64–80 kg), who were healthy as determined by medical history, physical examination and standard biochemical and haematological parameters. Subjects ab-

stained from methylxanthine-containing foods for 3 days prior to and during the study. No medications, other than those required for the study, were taken for 1 week before and during the study. The study details were fully explained to each subject who then gave written consent to participate. The study was approved by the Clinical Investigation and Drug and Therapeutics Advisory Committees at Flinders Medical Centre.

Each subject received theophylline (Nuelin-Riker) 125 mg orally every 8 h for 11 days. In addition, from days 5 to 11 the subjects took rifampicin (Rifadin-Protea) 600 mg with the morning dose of theophylline. On days 4 and 11, venous blood 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 0.1M acetic acid and kept at −20°C until analysed.

Analytical procedures

Theophylline plasma concentrations were determined using a fluorescence polarisation immunoassay (TDX, Abbott). Concentrations of unchanged theophylline and theophylline metabolites (1MU; 3MX; 1,3DMU) in urine were measured using high performance liquid chromatography (Grygiel *et al.*, 1979). In all assays the intra-assay co-efficients of variation were less than 7.0%

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:

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

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. Recoveries of theophylline-derived products in urine were 96.2 ± 2.0% (mean ± s.e. mean) in the control phase and 91.0 ± 7.1% in the rifampicin phase.

Table 1 Effects of rifampicin on metabolic and renal clearance of theophylline

Subject	CL[1]		CL_{1MU}		CL_{3MX}		CL_{DMU}		CL_R	
	T[2]	TR	T	TR	T	TR	T	TR	T	TR
1	0.606	1.280	0.178	0.353	0.071	0.246	0.279	0.596	0.072	0.084
2	0.646	0.829	0.169	0.244	0.110	0.147	0.280	0.369	0.088	0.069
3	0.700	1.624	0.188	0.473	0.097	0.296	0.342	0.741	0.074	0.115
4	0.772	1.163	0.195	0.342	0.103	0.186	0.366	0.545	0.107	0.090
5	0.865	1.875	0.254	0.551	0.151	0.326	0.381	0.849	0.078	0.163
6	0.881	1.347	0.242	0.391	0.133	0.234	0.403	0.624	0.101	0.098
Mean	0.745	1.353	0.204	0.392	0.111	0.239	0.342	0.621	0.087	0.103
s.e. mean	0.047	0.149	0.014	0.044	0.011	0.027	0.021	0.067	0.006	0.014
P	< 0.001		< 0.001		< 0.001		< 0.001		NS	

[1] Units of clearance are ml min^{-1} kg^{-1}

[2] T, theophylline alone; TR, theophylline plus rifampicin.

Results are expressed as mean ± s.e. mean. The signficance of differences between study phases was assessed using Student's *t*-test for paired samples and values of $P < 0.05$ were considered significant.

Results

The effects of rifampicin administration on theophylline total plasma clearance (CL) and on the renal and metabolic clearances of theophylline are summarised in Table 1. Rifampicin pretreatment increased CL by 82 ± 18%, from 0.745 ± 0.047 ml min^{-1} kg^{-1} to 1.353 ± 0.149 ml min^{-1} kg^{-1} ($P < 0.001$). The increase in CL was due to increases in CL_{1MU} (91 ± 16%, $P < 0.001$), CL_{3MX} (116 ± 34%, $P < 0.001$) and CL_{DMU} (81 ± 17%, $P < 0.001$). Renal clearance of unchanged theophylline was not significantly altered by rifampicin treatment. The attainment of steady-state on the 2 study days (days 4 and 11) was confirmed by trough concentrations within ± 10% at the beginning and end of the dosage interval on each study day.

Discussion

In this study pretreatment with rifampicin resulted in an 82% mean increase in theophylline plasma clearance, an effect similar in magnitude to that reported in a previous study in humans (Hauser *et al.*, 1983). This finding contrasts with the lack of effect of rifampicin treatment on theophylline metabolism in rabbits (Self *et al.*, 1982). The present study has also demonstrated that the increase in theophylline clearance due to rifampicin results from induction of all the theophylline metabolic pathways to a similar extent.

Rifampicin treatment is known to induce the clearance of antipyrine to norphenazone to a larger extent than to the other major antipyrine metabolites, suggesting that rifampicin selectively induces different forms of cytochrome P-450 (Toverud *et al.*, 1981). We have previously presented evidence that at least two forms of cytochrome P-450 are involved in theophylline metabolism, one mediating the demethylations to 1MX and 3MX and the second the 8-oxidation to 1,3DMU (Birkett *et al.*, 1982; Grygiel & Birkett, 1981). Cigarette smoking has been found to produce a greater induction of the demethylation pathways (Grygiel & Birkett, 1981) whereas sulphinpyrazone caused equal induction of all three metabolite pathways (Birkett *et al.*, 1983b). Rifampicin, like sulphinpyrazone, exerted a non-selective effect on theophylline metabolic clearances indicating that the two forms of cytochrome P-450 are induced to a similar extent.

The magnitude of the induction of rifampicin is similar to that observed in cigarette smokers (Grygiel & Birkett, 1981) but substantially greater than that due to sulphinpyrazone (Birkett *et al.*, 1983b) and phenobarbitone (Piafsky *et al.*, 1977). Average theophylline maintenance dose may need to be increased about 1.5 to 2-fold in patients who are taking rifampicin to achieve optimal therapeutic plasma concentrations and reduced if rifampicin is stopped during theophylline treatment.

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(*Received February 27, 1984, accepted May, 4, 1984*)