Lack of effect of flosequinan on the pharmacokinetics of theophylline

F. KAMALI, C. EDWARDS & M. D. RAWLINS

Wolfson Unit of Clinical Pharmacology, Claremont Place, The University, Newcastle upon Tyne NE1 7RU

The pharmacokinetics of theophylline (240 mg) p.o. were studied before and after the administration of oral flosequinan for 14 days in 21 healthy volunteers using a randomised cross-over design. Comparisons of $C_{\max}$, $t_{\max}$, AUC, CL of theophylline and urinary recovery of the parent drug and metabolites showed that flosequinan had no significant effect on the disposition of theophylline.

Keywords flosequinan quinolone theophylline drug interaction pharmacokinetics

Introduction

A number of quinolone antibacterial agents have been reported to lower the hepatic clearance of co-administered drugs that are metabolised by the cytochrome P-450 mixed function oxidases. A clinically significant decrease in the clearance of theophylline has been demonstrated with concurrent administration of ciprofloxacin (Schwartz *et al.*, 1988; Wijnands *et al.*, 1986), enoxacin (Beckmann *et al.*, 1987; Wijnands *et al.*, 1985) and pefloxacin (Niki *et al.*, 1987; Wijnands *et al.*, 1986). The mechanism of this inhibitory action of quinolones is not clear. It has been suggested that 4-oxo metabolites may play a role (Wijnands *et al.*, 1986), although this has been disputed (Edwards *et al.*, 1988).

Flosequinan, a 7-fluorinated quinolone, is a peripheral vasodilator, with effects on both the arterial and venous vasculature. It has no significant antimicrobial activity. It is possible that flosequinan, like other quinolones, may impair the hepatic elimination of those drugs that are metabolised by the P-450 system. This study was designed to investigate the possible effects of flosequinan on the metabolism and pharmacokinetics of theophylline in healthy volunteers.

Methods

Protocol

Twenty-one healthy volunteers (11 females) aged 18–23 years took part in the study which received approval from the Joint Committee of the University of Newcastle upon Tyne and Newcastle Health Authority. The study was designed as a randomised two-way crossover trial. Each volunteer received two treatments (A and B).

Treatment A comprised flosequinan 50 mg once daily for 3 days followed by 100 mg once daily for 10 days. On the fourteenth day (study day), each volunteer received flosequinan (100 mg) and an oral dose (240 mg) of theophylline solution. For treatment B, each volunteer received an oral dose (240 mg) of theophylline solution on the study day without pretreatment with flosequinan. There was at least a 25 day washout period between the 2 study days.

Subjects taking part in the study underwent a general medical examination and a 12 lead ECG on entry. A full serum biochemistry and haematology screen was performed before and after the study.

All volunteers were required to fast from 12 midnight before each study day. A glass of fruit juice or water was allowed on rising. In the morning of each study day, a cannula was inserted into a suitable forearm vein to facilitate blood sampling. Each volunteer then received his or her allocated medication with 100 ml of water whilst standing. Blood samples (5 ml) were collected before dosing and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10 and 24 h post-dose. Urine was collected immediately before (baseline) and for 24 h after the administration of theophylline. A cold, caffeine-free beverage and toast was provided after the 2 h blood sample had been withdrawn, and a standard lunch was provided after withdrawal of the 4 h blood sample. Subjects were required to abstain from taking xanthine-containing food or drinks 12 h prior to and 24 h after theophylline administration.

Assay

Following centrifugation of blood samples, plasma was separated and stored at -20°C until analysis for theophylline by high performance liquid chromatography

(h.p.l.c.) (Rodgers *et al.*, 1987). Pre-dose samples were analysed for caffeine (Rodgers *et al.*, 1987) as a measure of dietary compliance. An aliquot of urine was stored at -20°C until analysis for theophylline and its metabolites 3-methylxanthine (3MX), 1-methyluric acid (1-MU), 1,3-dimethyluric acid (1,3-DMU) and 1-methylxanthine (1-MX), as well as caffeine and one of its major metabolites, paraxanthine (1,7-dimethylxanthine) (Muir *et al.*, 1980). Measurement of theophylline in plasma and theophylline and its metabolites in urine was carried out within 1 month of sample collection. The intra-assay coefficient of variation for all measurements was less than 7%. Plasma concentrations of flosequinan and its major metabolite, flosequinan sulphone were measured at 0 h and 1 h on the study day (treatment A) using h.p.l.c. following solid phase extraction (Underwood & Hind, 1989). Briefly, 250 μl of plasma and 250 μl internal standard (BTS 49 037) ($1\text{ }\mu\text{g ml}^{-1}$) were applied to Bond Elut cartridges (Analytichem International, Ca. USA), washed with water (2 ml) and finally extracted with methanol (500 μl). An aliquot (100 μl) of the extract was then injected onto a C_{18} reverse phase 25 cm $\times$ 0.4 cm (5 μm particle size) column at 40°C . The mobile phase was water : methanol : acetonitrile (65 : 20 : 10, V/V/V) at a flow rate of 1.5 ml min^{-1} . Flosequinan, its metabolite and the internal standard were detected at 254 nm wavelength. The intra-assay coefficient of variation for flosequinan and its metabolite was less than 4%. The lower limit of assay was $0.05\text{ }\mu\text{g ml}^{-1}$ for both flosequinan and flosequinan sulphone.

Analysis of results

The area under the plasma theophylline concentration-time curve (AUC) was calculated by the trapezoidal rule with extrapolation to infinity using the terminal elimination rate constant (Kinetics 2, Apple software). Theophylline clearance was then calculated as dose/AUC and normalised for body weight.

The urinary recoveries of 1,3-dimethyluric acid, 1-methyluric acid, 3-methylxanthine and 1-methylxanthine

were expressed as total theophylline equivalents and the fractional excretion calculated as the percentage of total theophylline recovered in urine.

The results were analysed using a hierarchical analysis of variance (Brownlee, 1965) with factors for treatment order, volunteer within order, period of administration and treatment. The 95% confidence interval for the differences between the adjusted treatment means were also calculated. All results were expressed as the mean $\pm$ s.d. The value of $P < 0.05$ was taken to be statistically significant.

Results

The mean plasma theophylline-time profiles, with and without flosequinan pretreatment, are shown in Figure 1. The pharmacokinetic data and the urinary excretion of theophylline metabolites are presented in Table 1.

Figure 1 Mean ($\pm$ s.d.) plasma theophylline concentrations with ($\blacklozenge$) and without ($\square$) flosequinan pretreatment.

Table 1 Pharmacokinetic parameters for theophylline and fractional excretion of metabolites after administration of theophylline (240 mg) with and without flosequinan pretreatment in 21 subjects. Results are expressed as mean $\pm$ s.d.

	Control	Flosequinan treatment	95% confidence interval for difference between means
CL ($\text{ml min}^{-1} \text{ kg}^{-1}$)	0.92 ± 0.36	0.86 ± 0.33	$-0.14, 0.01$
AUC ($\mu\text{g ml}^{-1} \text{ min}$)	4615 ± 2358	4794 ± 2138	$-276, 703$
C_{max} ($\mu\text{g ml}^{-1}$)	8.7 ± 2.7	8.7 ± 2.2	$1.0, 1.1$
t_{max} (h)	1.1 ± 0.7	1.1 ± 0.6	
Total urinary excretion of theophylline (mg)			
	137.6 ± 40.1	134.3 ± 33.3	$-27.2, 20.4$
% fractional excretion of metabolites:			
1,3-Dimethyluric acid	41.4 ± 5.6	42.2 ± 6.8	$-2.4, 3.9$
1-Methyluric acid	19.4 ± 5.2	20.2 ± 6.6	$-2.4, 4.0$
3-Methylxanthine	17.2 ± 3.6	15.9 ± 5.7	$-3.9, 1.3$
1-Methylxanthine	4.1 ± 2.9	3.4 ± 2.1	$-2.0, 0.5$
Theophylline	18.1 ± 7.3	18.3 ± 8.3	$-3.1, 3.5$

Compared with control values, theophylline $t_{\max}$, $C_{\max}$, AUC and CL were not significantly different after pre-treatment with flosequinan. The fractional excretion of theophylline and its metabolites was also not affected by flosequinan.

Plasma caffeine and urinary 1,7-dimethylxanthine concentrations were negligible prior to theophylline administration in all subjects, demonstrating the adequacy of the dietary restrictions. Flosequinan was not detectable in the plasma at 0 h immediately before the final dose and its mean plasma concentration at 1 h was $1.1 \pm 0.8 \mu\text{g ml}^{-1}$. Plasma concentrations of the principal metabolite, flosequinan sulphone, were $4.4 \pm 1.3 \mu\text{g ml}^{-1}$ at 0 h and $4.7 \pm 1.1 \mu\text{g ml}^{-1}$ at 1 h. These data are in agreement with the plasma concentrations reported previously and

reflect the short elimination half-life of flosequinan (1.6 h) compared with the sulphone metabolite (37 h) (Wynne *et al.*, 1985). These data, together with tablet checks at 3 and 13 days, served to indicate satisfactory compliance by the volunteers. There were no significant changes in serum biochemistry and haematology at the end of the study.

Discussion

We conclude that flosequinan appears to be without effect on the pharmacokinetics of theophylline. It is therefore unlikely that a significant pharmacokinetic interaction will occur between these drugs in patients.

References

- Beckman, J., Elsaesser, W., Gundert-Remy, U. & Hertrampf, R. (1987). Enoxacin- a potent inhibitor of theophylline metabolism. *Eur. J. clin. Pharmac.*, **33**, 227-230.
- Brownlee, K. A. (1965). *Statistical theory and methodology in science and engineering*, 2nd edition, pp 482-489. N. Y: Wiley.
- Edwards, D. J., Waite, N. M. & Svensson, C. K. (1988). Effect of enoxacin and 4-oxo-enoxacin on antipyrine disposition in the rat. *Drug. Metab. Disp.*, **16**, 653-655.
- Muir, K. T., Jonkman, J. H. G., Tang, D. & Kunitani, M. (1980). Simultaneous determination of theophylline and its major metabolites in urine by reverse-phase ion-pair high performance liquid chromatography. *J. Chromatogr.*, **221**, 85-95.
- Niki, Y., Soejima, R., Kawane, H., Sumi, M. & Umeki, S. (1987). New synthetic quinolone antibacterial agents and serum concentration of theophylline. *Chest*, **92**, 663-669.
- Rodgers, A., Woodhouse, K. W. & Bateman, D. N. (1987). Effect of dosing and age on intravenous aminophylline pharmacokinetics. *Br. J. clin. Pharmac.*, **23**, 344-347.
- Schwartz, J., Jauregui, L., Lettieri, J. & Beckmann, K. (1988). Impact of ciprofloxacin on theophylline clearance and steady-state concentrations in serum. *Antimicrob. Agents Chemother.*, **32**, 75-77.
- Underwood, L. M. & Hind, I. D. (1989). A method for the simultaneous determination of flosequinan and its major metabolite in human plasma using high performance liquid chromatography. *Research Report*. Boots Pharmaceuticals, UK.
- Wijnands, W. J. A., Vree, T. B. & van Herwaarden, C. L. A. (1985). Enoxacin decreases the clearance of theophylline in man. *Br. J. clin. Pharmac.*, **20**, 583-588.
- Wijnands, W. J. A., Vree, T. B. & van Herwaarden, C. L. A. (1986). The influence of quinolone derivatives on theophylline clearance. *Br. J. clin. Pharmac.*, **22**, 677-683.
- Wynne, R. D., Crompton, E. L. & Hind, I. D. (1985). The pharmacokinetics and haemodynamics of BTS 49465 and its major metabolite in healthy volunteers. *Eur. J. clin. Pharmac.*, **28**, 659-664.

(Received 3 December 1990,
accepted 3 March 1991)