Effect of prednisolone on theophylline pharmacokinetics in patients with chronic airflow obstruction

R J FERGUSSON, CATHERINE M SCOTT, P RAFFERTY, J GADDIE

From the Medical Department, Peel Hospital, Galashiels

ABSTRACT The effect of prednisolone on the elimination kinetics of theophylline was studied in a group of nine patients with chronic airflow obstruction. Volume of distribution, plasma half life, and clearance after a single intravenous dose of aminophylline (5.6 mg/kg) were unchanged by prednisolone treatment (20 mg daily for three weeks). The metabolism of an intravenous bolus of theophylline is not influenced by oral prednisolone.

Theophylline is widely used as a bronchodilator for patients with airways obstruction. Its efficacy has been shown to relate directly to serum concentrations,¹ while toxic effects are commonly observed when the upper limit of the therapeutic range (10–20 µg/ml) is exceeded.² Clearly, any factor that influences the pharmacokinetics of theophylline, thereby altering serum concentrations, must be carefully controlled if the maximum clinical effectiveness of the drug is to be obtained without the risk of dangerous toxicity.

Studies of theophylline elimination in normal subjects have shown appreciable variations between individuals^{3,4} and many factors that alter the plasma clearance of the drug have been identified. Liver disease,⁵ congestive heart failure,⁶ severe airways obstruction,⁷ respiratory infection,^{7,8} and drugs (including erythromycin⁹ and cimetidine¹⁰) are known to decrease theophylline clearance. Cigarette smoking,¹¹ certain diets,^{12,13} and drugs such as phenobarbitone¹⁴ that induce hepatic microsomal enzymes increase the elimination of theophylline.

Many patients prescribed theophylline preparations for airways obstruction also take inhaled or systemic corticosteroids. Surprisingly little is known of the effect of the latter on theophylline pharmacokinetics. In 1979 Buchanan and colleagues¹⁵ briefly reported the development of theophylline toxicity in

three patients given large doses of hydrocortisone for severe acute asthma. By contrast, a recent study¹⁶ in healthy volunteers showed a significant increase in theophylline clearance during an infusion of corticosteroid. We have studied the effect of prednisolone on theophylline pharmacokinetics after an intravenous injection of aminophylline in nine patients with chronic airflow obstruction.

Methods

We studied nine patients (five of them men), aged 47–71 (mean 61) years, with chronic airflow obstruction. Five were ex-smokers, two current smokers, and two non-smokers. Five patients had positive skin test responses to common allergens and two had blood eosinophilia. Patients were only inhaling drugs— β agonists in nine cases, ipratropium in three, sodium cromoglycate in two, and steroids in five. All had shown spontaneous variability in FEV₁ of at least 20% at two previous clinic attendances and were considered suitable for a “trial” of prednisolone treatment. None had significant cardiac disease; one man had slightly abnormal results in liver function tests. No one was taking medications known to interact with theophylline. None of the five patients inhaling beclomethasone dipropionate received more than 400 µg per day.

Theophylline pharmacokinetics were studied on two separate occasions—before treatment with prednisolone (study 1) and during treatment with prednisolone (study 2). Beverages containing xanthine derivatives were not consumed for 12 hours before each study or at any time during the investigation.

Address for reprint requests: Dr J Gaddie, Peel Hospital, Galashiels TD1 3LQ.

Accepted 10 October 1986

Venous blood was taken for estimation of plasma urea and electrolyte concentrations. Liver function (serum bilirubin concentration and alkaline phosphatase, aspartate transaminase, and γ glutamyl transferase activities) and plasma theophylline concentration were determined before the start of the study.

Aminophylline 5.6 mg/kg (equivalent to 4.43 mg/kg of theophylline) in 60 ml normal saline was then infused intravenously over 15 minutes. Venous blood samples were drawn from the contralateral arm into heparinised tubes for determining plasma theophylline concentrations at 15 minutes (end of infusion): at 30, 45, 60, 90, 120, 150, and 180 minutes; and then hourly until eight hours after the start of the infusion.

The FEV₁ and forced vital capacity (FVC) were measured with a Vitalograph spirometer (best of three attempts) after the patient had had a 15 minute rest on arrival at the hospital and then 15, 30, and 60 minutes after the infusion. The pulse rate, measured by palpation of the radial artery, was also recorded at these times. Any side effects of the treatment were noted.

After the study the patients started treatment with enteric coated prednisolone tablets 20 mg daily for three weeks. The study was repeated at the end of this period while the patient was still receiving prednisolone. To check drug compliance, a known excess quantity of tablets was prescribed and the patient was asked to return all spare tablets at the end of the study.

Plasma theophylline concentrations were estimated by means of an enzyme immunoassay¹⁷ (EMIT), the coefficient of variation between two EMIT kits used with the same blood sample being 2%. The plasma half life ($t_{1/2}$) of theophylline was determined for each patient from the elimination phase (after 90 minutes) of the plasma concentration-time curve (figure) by linear regression. The apparent volume of distribution (Vd) was calculated by dividing the dose infused by the extrapolated value of plasma theophylline concentration at time zero. Plasma clearance (Cl) was calculated by the equation¹⁸

$$Cl = \frac{0.693 \times Vd}{t_{1/2}}$$

The paired Student's *t* test was used for statistical analysis.

All subjects gave informed consent to the study, which was approved by the ethical committee of the Borders Health Board.

Results

The elimination of theophylline during each eight hour study period is shown in the figure. The volume of distribution, plasma half life, and clearance did not differ significantly between study 1 and study 2 (table 1), showing that prednisolone had no influence on theophylline pharmacokinetics.

One patient, a 65 year old man, had slightly de-

Mean plasma theophylline concentration against time curves for each study.

Table 1 Theophylline pharmacokinetics for each study (mean values with standard deviations in parentheses)

	Before prednisolone	With prednisolone
Volume of distribution (l/kg)	0.50 (0.06)	0.52 (0.04)
Plasma half life (hours)	6.91 (1.9)	7.01 (1.6)
Plasma clearance (l/hour/kg)	0.0543 (0.01)	0.0541 (0.01)

ranged liver function, thought to be due to an excessive intake of alcohol. His plasma theophylline half life was higher (11.03 and 8.75 hours) and his clearance lower (0.032 and 0.047 l/kg per hour) than the mean values on each study day. The one current cigarette smoker showed a lower plasma half life (4.66 and 4.48 hours) and enhanced clearance (0.087 and 0.075 l/kg per hour) than the group as a whole.

The mean preinfusion FEV₁ increased from 0.89 to 1.251 after three weeks of prednisolone treatment. There was a similar small but insignificant rise in heart rate, FEV₁, and FVC after the aminophylline infusion (table 2). No adverse effects were observed at any stage during the study. All patients returned the correct number of prednisolone tablets when attending for study 2, suggesting that they had taken them correctly.

Discussion

Aminophylline and prednisolone are commonly used to treat patients with obstructive airways disease. It is therefore surprising that little is known about the effect of corticosteroids on the pharmacokinetics of theophylline,¹⁹ especially as the efficacy and safety of the latter drug depends on the maintenance of plasma concentrations within a narrow therapeutic range.^{1,2}

In 1979 Buchanan and colleagues¹⁵ described six patients who received a theophylline infusion for status asthmaticus. Toxic serum concentrations of theophylline developed when hydrocortisone was administered intravenously as a bolus, an effect not seen in the one control patient, who received saline. The validity of their conclusion that "a potentially important clinical drug interaction" had occurred has since been questioned by Leavengood *et al*¹⁶ on the grounds that the patients may have had severe bronchoconstriction or respiratory infection, factors known to decrease theophylline clearance.^{7,8} In an

attempt to eliminate these variables, they studied the effect of equivalent doses of methyl prednisolone and hydrocortisone on theophylline metabolism in seven healthy volunteers. Their results suggested that corticosteroids, far from decreasing theophylline elimination, actually increased it.

Our study, performed in outpatients with chronic airflow obstruction with some reversibility, showed that the metabolism of an intravenous bolus of theophylline was not influenced by oral prednisolone. Plasma theophylline clearance and half life after an intravenous infusion of theophylline was unchanged by three weeks' treatment with prednisolone 20 mg daily. The volume of distribution was also unaffected by steroid treatment. It seems unlikely that the small increase in mean preinfusion FEV₁ on day 2 influenced theophylline pharmacokinetics significantly.

Elimination of theophylline is largely by hepatic metabolism, only about 10% of the drug appearing unchanged in the urine.¹⁹ Antipyrine (phenazone) suffers a similar fate and is widely used as a model to study the activity of drug metabolising enzymes in the liver. Carefully designed studies have shown that corticosteroids can either increase,²⁰ decrease,²¹ or produce no change^{22,23} in plasma antipyrine half life, providing further evidence that the precise effect of corticosteroids on drugs metabolised by the liver remains unclear.

The results of our study suggest that the pharmacokinetics of an intravenous infusion of theophylline are uninfluenced by oral prednisolone in patients with chronic stable airflow obstruction. This may not, however, be the case if other factors, such as severe airways obstruction, respiratory infection, or hepatic dysfunction, are present.

We thank Mrs N Chapman for typing the manuscript.

References

- 1 Mitenko PA, Ogilvie RI. Rational intravenous doses of theophylline. *N Engl J Med* 1973;289:600-3.
- 2 Jacobs MH, Senior RM, Kessler G. Clinical experience with theophylline: relationship between dosage, serum concentration and toxicity. *JAMA* 1976;235:1983-6.
- 3 Jenne JW, Wyze MS, Rood FS, McDonald FM. Pharmacokinetics of theophylline. Application to adjust-

Table 2 FEV₁, forced vital capacity (FVC), and heart rate before and after theophylline infusion for each study (mean values with standard deviations in parentheses)

	Before prednisolone (study 1)		With prednisolone (study 2)	
	Before	After	Before	After
FEV ₁ (l)	0.9 (0.3)	1.1 (0.5)	1.25 (0.6)	1.35 (0.6)
FVC (l)	1.8 (0.6)	2.0 (0.8)	2.2 (0.9)	2.5 (0.8)
Heart rate (beats/min)	81 (11)	85.5 (13)	80 (6)	93.5 (22)

- ment of the clinical dose of aminophylline. *Clin Pharmacol Ther* 1972;**13**:349–60.
- 4 Mitenko PA, Ogilvie RI. Rapidly achieved plasma concentration plateaus, with observations on theophylline kinetics. *Clin Pharmacol Ther* 1972;**13**:329–35.
 - 5 Mangione A, Imhoff TE, Lee RV, Shum LY, Jusko WJ. Pharmacokinetics of theophylline in hepatic disease. *Chest* 1978;**73**:616–22.
 - 6 Piafsky KM, Sitar DS, Rangno RE, Ogilvie RI. Theophylline kinetics in acute pulmonary oedema. *Clin Pharmacol Ther* 1977;**21**:310–6.
 - 7 Powell JR, Vozeh S, Hopewell P, Costello J, Sheiner LB, Riegelman S. Theophylline disposition in acutely ill hospitalised patients. *Am Rev Respir Dis* 1978;**118**: 220–38.
 - 8 Fleetham JA, Nakatsu K, Munt PW. Theophylline pharmacokinetics and respiratory infections. *Lancet* 1978; ii:898.
 - 9 Kozak PP, Cummins LH, Gillman SA. Administration of erythromycin to patients on theophylline. *J Allergy Clin Immunol* 1977;**60**:149–51.
 - 10 Jackson JE, Powell JR, Wandell M, Bentley J, Dorr R. Cimetidine decreases theophylline clearance. *Am Rev Respir Dis* 1981;**123**:615–7.
 - 11 Powell JR, Thiercelin J, Vozeh S, Sansom L, Riegelman S. The influence of cigarette smoking and sex on theophylline disposition. *Am Rev Respir Dis* 1977;**116**: 17–23.
 - 12 Kappas A, Alvares AP, Anderson KE, *et al.* Effect of charcoal-broiled beef on antipyrine and theophylline metabolism. *Clin Pharmacol Ther* 1978;**23**:445–50.
 - 13 Kappas A, Anderson KE, Conney AH, Alvares AP. Influence of dietary protein and carbohydrate on antipyrine and theophylline metabolism in man. *Clin Pharmacol Ther* 1977;**20**:643–53.
 - 14 Landay RA, Gonzalez MA, Taylor JC. Effect of phenobarbital on theophylline disposition. *J Allergy Clin Immunol* 1978;**62**:27–9.
 - 15 Buchanan N, Hurwitz S, Butler P. Asthma—a possible interaction between hydrocortisone and theophylline [Letter]. *S Afr Med J* 1979;**56**:1147–8.
 - 16 Leavengood DC, Bunker-Soler AL, Nelson HS. The effect of corticosteroids on theophylline metabolism. *Ann Allergy* 1983;**50**:249–51.
 - 17 Gushaw JB, Hu MW, Singh P, Miller JG, Schneider RS. Homogenous enzyme immunoassay to theophylline in serum. *Clin Chem* 1977;**23**:1144.
 - 18 Rowland M, Tozer TN. *Clinical pharmacokinetics*. Philadelphia: Lea and Febiger, 1980:84.
 - 19 Ogilvie RI. Clinical pharmacokinetics of theophylline. *Clin Pharmacokinet* 1978;**3**:267–93.
 - 20 Flanagan RJ, Richens A. The influence of elevated plasma hydrocortisone concentrations on antipyrine metabolism in man. *Br J Clin Pharmacol* 1974;**1**: 409–12.
 - 21 Breckenridge A, Burke CW, Davies DS, Orme ML. Immediate decrease by hydrocortisone of the plasma half-life of antipyrine. *Br J Pharmacol* 1973;**47**:434–6.
 - 22 Elfstrom J, Lindgren S. Metabolism of phenazone in man after hydrocortisone administration. *Eur J Clin Pharmacol* 1978;**13**:69–72.
 - 23 Shively CA, Cagliardi CL, Hartshorn RD, Vesell ES. Failure of hydrocortisone to alter acutely antipyrine disposition. *Clin Pharmacol Ther* 1978;**23**:408–13.