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

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

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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, while toxic effects are commonly observed when the upper limit of the therapeutic range (10–20 μg/ml) is exceeded. 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 and many factors that alter the plasma clearance of the drug have been identified. Liver disease, congestive heart failure, severe airways obstruction, respiratory infection, and drugs (including erythromycin and cimetidine) are known to decrease theophylline clearance. Cigarette smoking, certain diets, and drugs such as phenobarbitone 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 colleagues briefly reported the development of theophylline toxicity in three patients given large doses of hydrocortisone for severe acute asthma. By contrast, a recent study 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.
Venous blood was taken for estimation of plasma urea and electrolyte concentrations. Liver function (serum bilirubin concentration and alkaline phosphatase, aspartate transaminase, and \( \gamma \) 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 FEV\(_1\) 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 immunoassay\(^{17}\) (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 equation\(^{18} \)

\[
Cl = \frac{0·693 \times Vd}{t_{1/2}}.
\]

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

<table>
<thead>
<tr>
<th></th>
<th>Before prednisolone</th>
<th>With prednisolone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume of distribution (l/kg)</td>
<td>0.50 (0.06)</td>
<td>0.52 (0.04)</td>
</tr>
<tr>
<td>Plasma half life (hours)</td>
<td>6.91 (1.9)</td>
<td>7.01 (1.6)</td>
</tr>
<tr>
<td>Plasma clearance (l/hour/kg)</td>
<td>0.0543 (0.01)</td>
<td>0.0541 (0.01)</td>
</tr>
</tbody>
</table>

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 FEV<sub>1</sub> increased from 0.89 to 1.25 after three weeks of prednisolone treatment. There was a similar small but insignificant rise in heart rate, FEV<sub>1</sub>, 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, especially as the efficacy and safety of the latter drug depends on the maintenance of plasma concentrations within a narrow therapeutic range.

In 1979 Buchanan and colleagues described six patients who received a theophylline infusion for status asthmaticus. Toxic serum concentrations of teophylline 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. on the grounds that the patients may have had severe bronchoconstriction or respiratory infection, factors known to decrease theophylline clearance. 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 FEV<sub>1</sub> 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. 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, decrease, or produce no change 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

3 Jenne JW, Wyze MS, Rood FS, McDonald FM. Pharmacokinetics of theophylline. Application to adjust-

Table 2  FEV<sub>1</sub>, forced vital capacity (FVC), and heart rate before and after theophylline infusion for each study (mean values with standard deviations in parentheses)

<table>
<thead>
<tr>
<th></th>
<th>Before prednisolone (study 1)</th>
<th>After prednisolone (study 1)</th>
<th>Before prednisolone (study 2)</th>
<th>After prednisolone (study 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV&lt;sub&gt;1&lt;/sub&gt; (l)</td>
<td>0.9 (0.3)</td>
<td>1.1 (0.5)</td>
<td>1.25 (0.6)</td>
<td>1.35 (0.6)</td>
</tr>
<tr>
<td>FVC (l)</td>
<td>1.8 (0.6)</td>
<td>2.0 (0.8)</td>
<td>2.2 (0.9)</td>
<td>2.5 (0.8)</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>81 (11)</td>
<td>85.5 (13)</td>
<td>80 (6)</td>
<td>93.5 (22)</td>
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