The Effect of Erythromycin on Theophylline Pharmacokinetics at Steady State*


We compared steady-state theophylline pharmacokinetics in 13 healthy adults before and immediately after erythromycin therapy. All subjects received a five-day course of oral aminophylline 3 mg/kg every six hours prior to and during a five-day course of oral erythromycin stearate (1 g daily). Each subject acted as his own control. Multiple serum samples were collected over ten hours following the last dose of aminophylline during both the control and experimental phases of the study. Erythromycin did not significantly affect theophylline clearance (P > 0.70), elimination (P > 0.75), or volume of distribution (P > 0.30). We found no evidence of a pharmacokinetic interaction between theophylline and erythromycin at steady state. Worsening pulmonary function may be responsible for altered theophylline pharmacokinetics in patients coincidentally receiving erythromycin.

Erythromycin has been reported to cause a significant increase in serum theophylline levels in reports involving asthmatic children.1,2 However, conflicting data exist, and investigators have been unable consistently to demonstrate a pharmacokinetic interaction between erythromycin and theophylline.9 In view of the lack of conclusive research regarding this potentially significant drug interaction, we conducted a controlled study to determine the effect of oral erythromycin on steady-state theophylline serum concentrations.

MATERIALS AND METHODS

Fourteen normal, healthy volunteers (nine men, five women) entered the study. The average age was 27 years (range, 23 to 33 years). Only one subject was a cigarette smoker. All individuals were given complete physical examinations prior to drug administration and were found to be free of identifiable diseases. No subjects received any medications other than theophylline and erythromycin during the study days. Approval for this study was granted by the University of Illinois Institutional Review Committee on Human Research. Informed consent was obtained from each subject.

The investigation was divided into two parts. In part 1 each subject received oral aminophylline, 3 mg/kg lean body weight, every six hours for five full days. Doses were rounded off to the nearest 50 mg. Venous blood samples were drawn at 0.5, 1.0, 1.5, 2.0, 3.0, 6.0, and 10 hours following the final dose of aminophylline on the fifth day. In part 2, each subject received aminophylline as described in part 1 plus oral erythromycin stearate, 250 mg four times daily. The erythromycin was taken concurrently with aminophylline for five full days. Venous blood samples were obtained at the end of the fifth day as in part 1. Serum was separated from all samples and frozen until the time of assay. Theophylline concentrations were determined by the EMIT assay (SYVA Co.). Twenty percent of the samples were randomly selected and double-checked using high-performance liquid chromatography following the method of Orcutt et al.4 There was no significant difference between results from these two methods (P > 0.5).

Apparent elimination rate constants (Ku) and half-lives (t½) were calculated from the theophylline serum concentration vs time curves. A best-fitting line was estimated for each subject using iterative nonlinear least-squares regression. The area under the serum concentration vs time curve (AUC) at steady state was estimated from theophylline serum levels using the trapezoidal rule.5 Steady-state clearance (Cl ss) and steady-state volume of distribution (Vd ss) were calculated* using standard pharmacokinetic methods.5,6 Differences in theophylline pharmacokinetic parameters (Cl ss, K u, t½, Vd ss) between parts 1 and 2 were assessed using the paired Student’s t test. (Cl ss = 0.84 × D/AUC ss, where Cl ss indicates steady-state theophylline clearance, D is the dose of oral aminophylline given every six hours, and AUC ss is the area under the serum concentration vs time curve at steady state. Vd ss = Cl ss/K u, where Vd ss is the volume of distribution at steady state, and K u is the elimination rate constant).

RESULTS

One subject was dropped from the study due to poor compliance with the dosing regimen. The re-
remaining 13 subjects completed their courses of aminophylline and erythromycin as directed and were compliant with each regimen. Compliance was assessed by tablet counts and interviews with each subject. Twelve of 13 subjects (92 percent) reported moderate side effects (nausea, headaches, and tremulousness), which occurred with equal frequency in both parts of the study. The occurrence of these side effects was associated with peak theophylline serum levels. The maximum serum concentration observed in any subject was 17 µg/ml.

Steady-state theophylline clearances for each subject are depicted in Figure 1. The differences in steady-state clearances for parts 1 and 2 are not significant (P > .70). Similarly, steady-state volume of distribution and elimination half-lives in parts 1 and 2 are not significantly different (Table 1).

**Discussion**

The effect of erythromycin on theophylline pharmacokinetics has not been well characterized. Troleandomycin (TAO), a macrolide antibiotic similar in structure to erythromycin, has been shown to cause a significant decrease in theophylline elimination, resulting in notably increased serum concentrations. TAO is thought to decrease theophylline clearance by decreasing hepatic uptake or by altering hepatic degradation. Erythromycin may have a similar effect on theophylline elimination, although the only data initially supporting this belief were provided by a series of case reports, one uncontrolled study, and an unpublished controlled trial in a limited number of subjects.

Zarowitz et al recently conducted a controlled trial examining the effect of a ten-day course of erythromycin base on theophylline kinetics. The authors concluded that erythromycin results in a decrease in theophylline clearance. This conclusion was supported by a significant difference (P < 0.05) between clearances measured on the tenth day of erythromycin and again two weeks following the last dose of erythromycin. Unfortunately, theophylline clearance prior to beginning the course of antibiotic was not significantly different from that measured on the tenth day of therapy. In view of this inconsistency, one must question the authors' conclusions.

Other recent investigations have suggested that there are no significant changes in theophylline pharmacokinetics during erythromycin therapy. These studies have not provided an answer to the controversy. Pfeifer et al studied nine subjects who received erythromycin for only 24 hours prior to the administration of a single intravenous (IV) dose of aminophylline. Theophylline pharmacokinetics were not significantly altered by erythromycin in this study. Because theophylline was not allowed to reach steady state, these data do not exclude the possibility of a pharmacokinetic interaction's occurring with long-term therapy. In addi-

**Table 1—Mean Theophylline Pharmacokinetic Values of the 13 Subjects Studied in Parts 1 and 2**

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Part 1, Theophylline Alone</th>
<th>Part 2, Theophylline Plus Erythromycin</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Ke (hr⁻¹)</td>
<td>0.79</td>
<td>0.76</td>
<td>&gt;0.70</td>
</tr>
<tr>
<td>SD</td>
<td>.026</td>
<td>.093</td>
<td></td>
</tr>
<tr>
<td>Mean Clₚ (L/hr/kg)</td>
<td>.046</td>
<td>.047</td>
<td>&gt;0.75</td>
</tr>
<tr>
<td>SD</td>
<td>.015</td>
<td>.017</td>
<td></td>
</tr>
<tr>
<td>Mean Vp₂ (L/kg)</td>
<td>.55</td>
<td>.60</td>
<td>&gt;0.30</td>
</tr>
<tr>
<td>SD</td>
<td>.11</td>
<td>.19</td>
<td></td>
</tr>
</tbody>
</table>

*Abbreviations: Ke, elimination rate constant; Clₚ, steady-state clearance; and Vp₂, steady-state volume of distribution.
tion, previously available data suggest that longer than 24 to 48 hours of concurrent macrolide therapy may be required before an effect on theophylline pharmacokinetics is observed. Pingelton et al. studied eight normal adult volunteers given oral erythromycin and IV aminophylline for unspecified periods. Serum theophylline levels were not affected by the concomitant erythromycin therapy. However, the complete details of this investigation have not been published for review at this time. Administration of IV erythromycin did not alter theophylline clearance in one patient described by Kimelblatt and Slaughter, although it is difficult to draw general conclusions from this single case report.

Although many investigators have postulated that erythromycin directly affects theophylline elimination, our data do not support this contention. The present study examines theophylline pharmacokinetics after five days of concurrent erythromycin therapy, allowing both drugs to attain steady-state levels. This method of drug administration also closely simulates a clinical setting in which erythromycin treatment is instituted in patients receiving maintenance oral theophylline therapy. Our results, obtained under controlled conditions, demonstrate that erythromycin has no effect on theophylline pharmacokinetics in normal subjects at steady state.

A possible explanation for the altered theophylline elimination observed in patients receiving concomitant erythromycin may be related to acute changes in pulmonary function. It has been demonstrated that severe pulmonary disease influences drug kinetics. Acute episodes of severe obstructive airway disease, pneumonia and acute viral illness may decrease theophylline clearance. Many asthmatic patients with these complications are given erythromycin for suspected infection. This suggests that erythromycin therapy may be a correlate of worsening pulmonary function (and decreased theophylline clearance) rather than a direct cause of altered theophylline elimination. This explanation would account for our inability to detect any significant change in theophylline disposition during erythromycin therapy in normal subjects.

**Conclusion**

We have shown that theophylline pharmacokinetics are not altered by concurrent erythromycin administration. This controlled study was performed in 13 normal volunteers under steady-state conditions. Our findings agree with previous data for normal volunteers, leading us to believe that erythromycin itself is not responsible for the observed changes in theophylline pharmacokinetics. We postulate that severe pulmonary disease often coincident with erythromycin therapy is the more likely cause of decreased theophylline elimination.

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**REFERENCES**