The Effect of Erythromycin on Theophylline Pharmacokinetics in Chronic Bronchitis[1,2]

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SUMMARY We examined theophylline pharmacokinetics for changes caused by the addition of erythromycin in patients with chronic bronchitis and obstructive pulmonary disease. Twelve hospitalized patients were randomized in a crossover fashion to receive aminophylline and either erythromycin or placebo. After the eighth dose, plasma was analyzed for theophylline, using the enzyme-mediated immunoassay technique. A 6-h urine collection was analyzed for theophylline metabolites, using high-pressure liquid chromatography. Erythromycin significantly decreased mean theophylline clearance by 22% from 4.9 L/min to 3.87 L/min ($p < 0.05$). Mean peak theophylline levels increased 28% from 11.9 μg/ml to 15.3 μg/ml ($p = 0.05$). No change in urine theophylline metabolites was found. Patients with chronic bronchitis and obstructive pulmonary disease who begin erythromycin while receiving a preexisting therapeutic theophylline regimen experience a significant elevation of theophylline concentration, which predisposes to theophylline toxicity. For those patients with theophylline levels at the higher end of the therapeutic range (15 to 20 μg/ml), we recommend an initial 25% reduction in theophylline dosage when erythromycin is added. Serum theophylline levels should be monitored for further refinement of dosage.

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Introduction

Theophylline compounds are a primary form of treatment in patients with chronic bronchitis and obstructive pulmonary disease. When acute infectious complications arise, antibiotics are frequently added, and erythromycin is often chosen in this clinical setting. Recent studies have raised the question of a possible erythromycin-theophylline interaction (1-8). Although some of the investigators have found the addition of erythromycin to result in a decreased theophylline clearance (1-5), others have been unable to confirm this (6-8).

Although several erythromycin preparations exist (base, estolate, succinate, stearate), it does not appear that the differences can be entirely explained on this basis. Theophylline pharmacokinetic changes have been noted in all preparations (1, 2). The duration of erythromycin-theophylline therapy has also been incriminated. Studies where the duration of erythromycin therapy was less than 5 days have shown no alteration of pharmacokinetics (6-8). Other studies where erythromycin has been given for 7 to 14 days have demonstrated pharmacokinetic changes (2-5). On the basis of these studies, Jenne (9) has recommended an adjustment of theophylline levels into the lower end of the therapeutic range to diminish the possibility of theophylline toxicity when erythromycin is added. All of these studies, however, have been in either normal adults or asthmatic children. It is well recognized that disease states such as pneumonia, heart failure, and critical illness may alter theophylline kinetics (10, 11). Hypoxia alone has been suggested to alter theophylline metabolism (12). The pharmacokinetic effect of a theophylline-erythromycin interaction in chronic bronchitis and obstructive pulmonary disease has not been examined in a crossover fashion. Recommended alterations may or may not be applicable to the chronic bronchitic with air-flow obstruction. The purpose of our study was to examine the effect of erythromycin on theophylline pharmacokinetics in adults with stable chronic bronchitis and obstructive pulmonary disease. We also examined urinary theophylline metabolites before and after the addition of erythromycin.

Methods

Twelve patients, 8 men and 4 women, were studied. They ranged from 27 to 72 yr of age, with a mean age of 54 yr. All patients had chronic bronchitis, as defined by a productive cough on most days for at least 3 months of the year in 2 consecutive years. All patients had stable, mild-to-moderate pulmonary disease as defined by a forced expiratory volume in one second (FEV_1) to forced vital capacity (FVC) ratio less than 75% and an absolute FEV_1 greater than 1 L. The patients were free of known active cardiac or hepatic dysfunction, and they did not have any respiratory infections in the month preceding the study. Informed consent, as approved by Truman Medical Center and the University of Missouri-Kansas City School of Medicine Human Experimentation Review Committees, was obtained from each patient.

All patients were admitted to the hospital on Day 1 to ensure compliance. A history, physical examination, serum aspartate aminotransferase, lactic dehydrogenase, alkaline phosphatase, and electrocardiogram were done to rule out active cardiac or hepatic disease. The diet was a standard xanthine-free diet given 1 h after medications. There were no medical changes in the month preceding the study, and the patients continued taking their usual medicine (with the exception of theophylline products) throughout the study. Each patient was then randomized to one of two crossover protocols. Six patients received erythromycin stearate (Abbott Laboratories, Chicago, IL) 500 mg orally every 6 h, whereas the other 6 received placebo. Each patient received aminophylline HCl (Searle Analytical, Inc., Des Plaines, IL) 4 mg/kg orally every 6 h. After the eighth dose of aminophylline plus erythromycin or aminophylline plus placebo, multiple blood samples were collected in a heparinized tube at 0, 0.5, 1, 2, 3, 4, 6, 8, 10, and 12 h. The blood was immediately centrifuged and the plasma separated. A 6-h urine collection

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was obtained after the eighth dose. The urine and plasma samples were frozen at −20° C until assayed. The subjects were then discharged from the hospital for the washout period and readmitted on Day 9. Erythromycin-placebo crossover occurred during the second phase of the study. The blood and urine were collected and processed on Day 11, as before.

Plasma theophylline levels were quantitatively analyzed using the enzyme-mediated immunoassay technique (EMIT) (13). The EMIT method is specific for theophylline in the presence of metabolites (14). Individual time versus plasma theophylline concentration curves were drawn by linear regression. Area under the curve for the dosing interval of 0 to 6 h (AUC_{0-6}) was calculated from the individual time-theophylline curve using the trapezoidal rule, and half-life was taken from the terminal slope of the time-theophylline curve (15). Theophylline clearance (Cl) was then calculated using the formula $Cl = dose/AUC_{0-6}$. The urine was analyzed for theophylline, 3-methylxanthine, 1-3 dimethyluric acid, and 1-methyluric acid using high pressure liquid chromatography (16). Statistical significance was determined using analysis of variance (17).

Results

One patient (Subject 8) became nauseated during the first phase of the study while receiving erythromycin and aminophylline. Both drugs were stopped and an immediate plasma theophylline concentration was 27 μg/ml. Insufficient time was available for this patient to reach steady state at a lower aminophylline dose. Therefore, his participation in the study was terminated.

The addition of erythromycin affected the plasma theophylline concentration at several time intervals (figure 1). Mean plasma concentrations were higher in the presence of erythromycin, and this difference was significant at 1 and at 4 h ($p < 0.05$). The 1-h mean plasma theophylline concentration rose 52%, from 9.4 μg/ml to 14.3 μg/ml, in the presence of erythromycin. The 4-h mean level rose 26% from a baseline of 7.8 μg/ml to 9.9 μg/ml with erythromycin. The theophylline concentration at 30 min, and 2, 3, 6, 8, 10, and 12 h did not differ significantly. The line connecting data points was drawn by visual approximation.

Peak plasma theophylline concentration, theophylline clearance, and theophylline half-life with aminophylline alone and with aminophylline plus erythromycin, are shown in table 1. The peak theophylline concentration was higher while taking erythromycin in all 11 patients. The mean peak theophylline concentration increased an average of 28% from 11.0 μg/ml to 15.3 μg/ml ($p = 0.0502$). Theophylline clearance decreased in 10 of 11 patients in the presence of erythromycin. Changes in clearance ranged from +8% to −44%. Mean clearance decreased by 22% from 4.9 L/h with aminophylline alone to 3.87 L/h with aminophylline plus erythromycin ($p < 0.05$). Changes in theophylline half-life with the addition of erythromycin were more variable. Half-life decreased in 5 patients, increased in 5 patients, and was essentially unchanged in 1 patient. Urinary theophylline metabolites are shown in table 2 for each patient with aminophylline alone and with aminophylline plus erythromycin. The percentages are given as percent of urine theophylline and theophylline metabolites recovered. The addition of erythromycin produced no significant alteration in the percent of urinary theophylline, 3-methylxanthine, 1-3 dimethyluric acid, or 1-methyluric acid recovered.

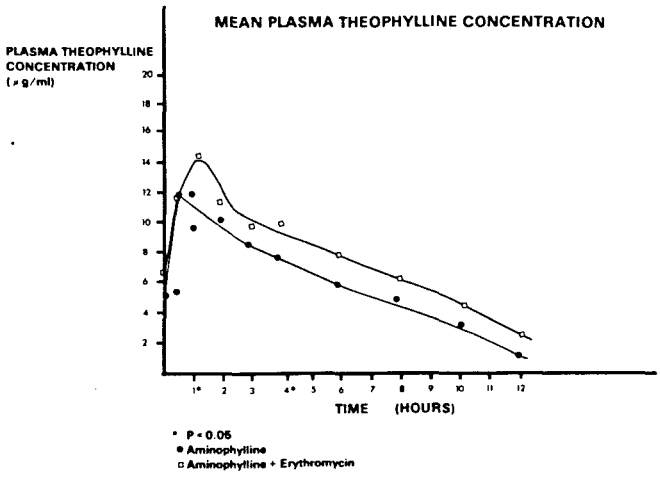

Fig. 1. Mean plasma theophylline concentrations are plotted against time for aminophylline alone and aminophylline plus erythromycin.

Discussion

Concomitant use of erythromycin and theophylline is increasing as physicians become more aware of the role of erythromycin-sensitive organisms, such as *Mycoplasma* and *Legionella* in acute bronchitis and pneumonia (18). At the same time, data are beginning to accumulate that suggest erythromycin alters theophylline kinetics. Any erythromycin-induced elevation of theophylline concentrations could increase the risks of theophylline toxicity.

Erythromycin-induced elevations of plasma theophylline concentrations were first found in asthmatic children (1). Conflicting data followed when erythromycin-theophylline interactions

TABLE 1

THEOPHYLLINE KINETICS WITH AMINOPHYLLINE (A) AND AMINOPHYLLINE PLUS ERYTHROMYCIN (A+E)*

Subject No.†	Peak Plasma Theophylline, (μg/ml)		Theophylline Clearance, (L/h)		Theophylline Half-life	
	A	A+E	A	A+E	A	A+E
1	8.70	13.0	9.80	5.44	6.24	4.62
2	10.0	14.5	3.68	3.26	4.65	10.6
3	13.0	13.8	5.18	3.75	5.13	7.99
4	15.5	18.5	2.22	1.82	11.4	11.2
5	12.2	23.0	4.47	2.72	5.68	6.50
6	11.0	11.6	5.56	6.02	4.85	4.08
7	12.5	13.3	5.58	3.86	5.41	5.46
9	14.5	16.0	3.00	2.53	5.59	6.73
10	9.50	13.0	5.80	5.32	7.11	6.66
11	11.5	12.6	5.87	4.83	5.97	5.97
12	13.0	19.0	3.18	2.97	5.87	5.70
Mean	11.9 ± 2.08	15.3 ± 3.50	4.94 ± 2.05	3.87 ± 1.37	6.17 ± 1.86	6.87 ± 2.26
	$p = 0.05$		$p < 0.05$		NS	

* Changes in theophylline peak plasma concentrations, clearance, and half-life caused by erythromycin are shown.
† Subject No. 8 became clinically toxic while taking erythromycin and aminophylline, and did not complete the protocol.

TABLE 2

URINARY THEOPHYLLINE METABOLITES AS PERCENT OF METABOLITES RECOVERED FOR AMINOPHYLLINE (A) AND AMINOPHYLLINE PLUS ERYTHROMYCIN (A + E)*

Subject No.†	Theophylline		3-methylxanthine		1-3 dimethyluric acid		1-methyluric acid	
	A	A+E	A	A+E	A	A+E	A	A+E
1	5.12	4.91	17.1	16.8	49.6	49.8	28.2	28.5
2	7.16	7.65	14.8	13.2	49.4	50.9	28.6	28.3
3	19.4	1.38	13.9	14.3	41.3	51.5	25.2	32.8
4	11.9	9.81	14.2	12.7	42.0	52.9	31.9	24.6
5	5.05	9.64	15.2	12.0	49.2	56.2	30.5	22.7
6	8.58	7.49	15.8	13.8	48.8	50.2	26.8	28.5
7	6.02	12.6	16.9	14.5	45.3	45.0	31.8	27.9
9	19.8	12.3	8.24	10.4	39.1	37.4	33.0	39.2
10	11.6	26.1	18.6	10.9	41.7	41.9	28.0	21.1
11	13.4	13.8	18.1	12.6	39.0	42.8	29.5	30.9
12	4.98	6.14	12.4	16.1	51.0	49.7	31.6	28.1
Mean	10.3 ± 5.49	10.2 ± 4.42	15.0 ± 2.93	14.8 ± 2.47	45.1 ± 4.61	48.0 ± 5.58	29.6 ± 2.45	28.4 ± 5.47
	NS		NS		NS		NS	

* There was no significant alteration of urinary theophylline metabolites with the addition of erythromycin.
† Subject No. 8 became clinically toxic while taking erythromycin and aminophylline, and did not complete the protocol.

were studied in normal adults. Presently, 3 studies have found that erythromycin decreased theophylline clearance (2, 3, 6), whereas 3 other studies did not find any significant effect (6–8). The form of erythromycin used does not appear to be responsible for the differences in results, as multiple forms of erythromycin, including base, estolate, succinate, and stearate, have been found to affect theophylline kinetics (1, 2, 5). Also, the variable bioavailability of oral erythromycin does not appear to completely explain the different results, as intravenously administered erythromycin lactobionate failed to alter theophylline pharmacokinetics in one study (19).

The effect of erythromycin on theophylline pharmacokinetics may not be immediate, and this may explain the different results found among the studies of normal adults. Those that found a significant decrease in theophylline clearance used erythromycin given for a longer period, 7 to 10 days (3, 5, 8), compared with those in studies that found no significant effect after giving erythromycin for only 1 to 5 days (6–8). Richer and coworkers (20) recently reported that erythromycin for 5 days decreased theophylline clearance in patients with asthma, but they found no effect in patients with chronic air-flow obstruction. The reason no difference was seen in patients with chronic air-flow obstruction may relate to the smaller number of subjects (8) and to the lack of crossover design in the study. Using a crossover design in 12 patients, we found a consistent and significant alteration of theophylline pharmacokinetics after only 2 days of erythromycin administration. Peak plasma theophylline concentrations increased in all 11 patients and theophylline clearance decreased in 10 of 11 patients. The alteration in theophylline kinetics were shown to occur earlier (after only 2 days of erythromycin) than in previous studies (3–5, 8, 20). Because a study by our group using an identical protocol failed to find any alteration of theophylline kinetics in normal subjects (7), our data from this study of patients with chronic bronchitis and obstructive pulmonary disease suggest that the effect of erythromycin on theophylline kinetics may occur earlier in these patients than in normal subjects.

Although the mean theophylline half-life increased 11% with the addition of erythromycin, this change did not reach significance. The increase in half-life was not proportionate to the decrease in clearance caused by erythromycin. As clearance and half-life are related by the formula

$$Cl = \frac{\text{volume of distribution} \times 0.693}{t\ ½}$$

our findings suggest a decrease in the volume of distribution. This is in contrast to the work of Prince and associates (3), who found essentially equal changes in the half-life and clearance, and, therefore, believed the volume of distribution to be unchanged by erythromycin. Like Prince and associates, however, we did not directly measure volume of distribution. It remains for further studies to verify whether changes in the volume of distribution may, in whole or part, explain the changes found in theophylline pharmacokinetics.

Urinary theophylline metabolites were analyzed to investigate the possibility of altered metabolic pathways as a possible cause for the change in kinetics. The finding of Danan and coworkers (21) that erythromycin increased the amount of inactive cytochrome P-450 in rats supports this theory. Because this effect was time and dose dependent, these data fit well with the studies in humans, demonstrating an effect only after erythromycin was given for several days (3–5, 8, 20). There was, however, no statistical change in the urinary metabolites recovered. It should be noted that we recovered an average of 75% of the given dose as urinary metabolites.

There are several possible explanations for the suboptimal recovery of theophylline metabolites. One likely explanation is incomplete voiding or collection of urine despite the patients being hospitalized and assisted with their urine collection. Theophylline has been shown to be virtually 100% absorbed (22), and it is unlikely that erythromycin would interfere with this absorption in view of the elevated plasma theophylline concentrations caused by erythromycin.

We do not know specifically how erythromycin alters theophylline kinetics. If erythromycin selectively inhibits theophylline metabolism, there should be a quantitative alteration of metabolites. If erythromycin exerts a nonselective inhibition of theophylline metabolism, the relative amount of unmetabolized theophylline recovered in the urine should increase. These

changes were not found. A decrease in the volume of distribution, as suggested by the disproportionate changes in half-life and clearance, could explain the increased plasma concentrations and decreased clearance without necessarily altering urine theophylline metabolites, but this was not measured directly. It is impossible to draw firm conclusions from this small study on the method by which erythromycin alters theophylline kinetics; rather, we can only say that we found no quantitative alteration of urine theophylline or theophylline metabolites recovered.

We believe our results are directly applicable to clinical practice, as our study was designed to simulate the most common clinical situation: the patient with chronic bronchitis and obstructive pulmonary disease taking medications orally at steady state. Because the toxic effects of theophylline increase with higher theophylline concentrations (23, 24), decreased clearance should increase theophylline toxicity. Only Patient 8 in our study became clinically toxic while taking erythromycin and aminophylline, and he did not complete the crossover phase of the protocol. The low incidence of toxicity in our study was thought to be related to the low baseline theophylline concentrations for aminophylline alone (mean peak theophylline concentration, 11.0 μg/ml) compared with the normal therapeutic range of 10 to 20 μg/ml (25). Indeed, the changes we found studying the stable patient may be even greater in the setting of an acute infection, as theophylline half-life may be prolonged with pneumonia (10), viral upper respiratory infections (26), and fever (27). In addition, we may not have seen the maximal effect of erythromycin. It is reasonable to suspect that erythromycin given in larger doses (as with *Legionella* infections) or given longer than 2 days may have an increased effect.

Patients taking theophylline compounds, especially those patients with higher therapeutic concentrations, as recently recommended (28), are at risk to develop theophylline toxicity when erythromycin is added. Because of the significant decrease (22%) in theophylline clearance with erythromycin, we recommend an initial 25% reduction in theophylline dose if the patient is known to have a "higher" (15 to 20 μg/ml) therapeutic theophylline level. We recognize that, because of the wide intersubject variation, some patients may deserve a greater reduction in dose and others may require no reduction. A 25% decrease represents an initial approximation of theophylline dosing reduction. Further monitoring with theophylline levels as therapy progresses would be required for refinement of the dose. For patients known to be or dosed to be on the lower end of the therapeutic range (8 to 15 μg/ml), little adjustment appears necessary unless symptoms develop.

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