Theophylline
A Remarkable Window to the Hepatic Microsomal Oxidases

Theophylline, if not exactly a window to the soul, has become a remarkable tool to expose the vagaries of hepatic microsomal oxidative enzyme function in man. The wide use of this drug in differing circumstances, coupled with the widespread practice of measuring its serum levels, has inadvertently resulted in fascinating insights into its disposition that can be applied to other drugs using the same oxidative elimination pathways.

The concurrent use of theophylline and erythromycin may be on the increase. In this issue, Maddux et al (see page 563) have examined the contention that erythromycin impairs theophylline clearance, reaching a negative conclusion. In 13 normal adults, 250 mg of erythromycin stearate for five days did not alter mean theophylline clearance. The issue arose from retrospective case reports of elevated theophylline levels in asthmatic children receiving various salts of erythromycin during respiratory infections¹,² and the marked reduction in theophylline clearance reported in patients receiving troleandomycin, a related but hepatoxic macrolid antibiotic.³ Heretofore, most prospective studies of the erythromycin question have used 24 hours or less of erythromycin, with less time to alter clearance mechanisms. However, Prince et al⁴ found a mean reduction of 27.7 percent in theophylline clearance in eight patients after one week of erythromycin base. In a study released just before submission of the Maddux report, Zarowitz et al⁵ reported a mean reduction of 12 percent in theophylline clearance after a ten-day course of erythromycin base in eight adults, significantly less when compared to the clearance 14 days later, but not when compared to the initial or third day clearance. There now have followed two reports with more positive results. In 15 asthmatic children receiving a larger mean dose of 24 mg/kg/day erythromycin ethyl-succinate for seven days, LaForce et al⁶ found a 35.8 ± 18 percent mean reduction in clearance, and a 40 ± 35.5 percent increase in theophylline levels. Renton et al⁷ found that erythromycin base at a dose of 250 mg q 8 hours given to 12 healthy adults for one week increases theophylline half life from 4.78 ± 0.43 to 7.53 ± 0.71 hours with a commensurate reduction in clearance but no change in distribution volume. Analysis of urine theophylline metabolites in three subjects revealed an appropriate reduction in the proportion of 3-methylxanthine and 1,3 dimethyluric acid to unchanged theophylline. Thus, in spite of the obviously competent study by Maddux et al, there are at least three longterm studies showing an appreciable interaction,⁴,⁶,⁷ and one a marginal effect.⁵ One is forced to conclude that both adults and children tend to alter oxidative metabolism of theophylline during a course of erythromycin base or its salts, although not to the extent shown with troleandomycin.

The Renton report is particularly significant in view of the involvement of these authors in a totally different phenomenon that might easily have been adduced to explain the entire problem of elevation of theophylline levels in patients with viral infections placed on erythromycin. Over the last five years, a series of investigations exploring the interrelationship of interferon induction and drug metabolism has demonstrated that a variety of agents, all having in common the ability to induce interferon, depress the activity of the hepatic cytochrome P-450 dependent mono-oxygenase systems.⁸ Indeed, endotoxin, BCG, Corynebacterium parvum, and Plasmodium berghei are included in the list of agents capable of producing this result. This is the apparent explanation by Chang et al⁹ in influenza A infection, and now in influenza B infection reported by Kraemer et al,¹⁰ although fever per se may be a factor.¹¹ A prospective study by Renton et al¹² from the original group of pharmacologists studying this phenomenon has shown that influenza vaccination can double theophylline levels and cause theophylline toxicity. It now appears that patients placed on therapy with erythromycin dur-
ing viral infections have at least two causes for elevated theophylline levels.

There are other interesting developments in the area of oxidative degradation of drugs that have been stimulated by observations with theophylline. The reports of acceleration of its clearance by cigarette smoking were one of the first insights into the instability of oxidative pathways of a therapeutic drug. A simultaneous observation was made with smoking and antipyrene clearance. Later, the effect of diet on theophylline metabolism was shown by Kappas et al and Alvares et al. An increase in carbohydrate content prolonged theophylline's half-life, while an increase in protein content shortened it. This effect assumed outrageous proportions with the recent demonstration by Feldman et al in 14 children that a high-protein diet of 3.0 g/kg and 65 percent carbohydrate for 12 days shortened the half-life to 4.74±1.21 hours, while a diet of 0.5 g of protein per kg and 78 percent carbohydrate prolonged the half-life to 18.1±7.72 hours! These values were compared with a half-life of 8.78±1.79 hours on the usual diet of 1.2 g of protein per kg and 60 percent carbohydrate. These diet studies raise the question of the effect on theophylline metabolism of prolonged starvation or intravenous fluid therapy. Studies in the respiratory intensive care situation have not totally dissected the processes involved in the often impaired initial theophylline clearance and its normalization during recovery. The effects of hypoxemia alone must be studied.

To add to this potpourri is the recent quantitation of the substantial effect of cimetidine in prolonging theophylline's half-life, a doubling in the average case, further confirming the observation that cimetidine inhibits microsomal oxidative metabolism of drugs with effects on diazepam, antipyrene, and warfarin-like compounds as well.

In view of the unpredictability of these effects, and the problems occasionally encountered with the more generally recognized host factors, it seems prudent in most cases to adjust theophylline levels into the lower end of the "therapeutic range," i.e., 8 to 15 μg/ml, and relay on bronchodilator combinations when more vigorous bronchodilation is needed.

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References