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Technical Note

Pharmacokinetics of Pentoxifylline During Concomitant Theophylline Administration to Rats

Mario L. Rocci, Jr.,[1,3] David R. Luke,[3] and Consuelo L. Saccar[2]

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INTRODUCTION

Pentoxifylline is a trisubstituted xanthine derivative currently being employed as a primary treatment for peripheral arterial occlusive disease (1). Pentoxifylline is structurally related to the bronchodilator theophylline. Each compound possesses a xanthine nucleus and a methyl group at the 3 position.

Theophylline elimination in humans occurs through a variety of metabolic processes including (a) hydroxylation to form 1,3-dimethyluric acid (which accounts for approximately 39% of the administered dose), (b) N-demethylation and hydroxylation to form 1-methyluric acid (which accounts for 20% of the administered dose), and (c) N-demethylation to form 3-methylxanthine (which accounts for approximately 16% of the administered dose) (2). In addition, theophylline N-methylation to caffeine has been observed in neonates and accounts for less than 10% of the theophylline dose (3,4).

As with theophylline, N-demethylation has been documented for pentoxifylline (although at a different position on the xanthine nucleus); extensive metabolism of the oxohexyl side chain has also been observed (5–10). Metabolites analagous to a and b above might be expected for pentoxifylline based on its structural resemblance to theophylline.

The similarities in structure between pentoxifylline and theophylline suggest that they may share common metabolic pathways and compete for hepatic drug metabolizing enzymes during their coadministration. Such a drug interaction could have clinical relevance in patients receiving these drugs in the treatment of chronic obstructive airway disease and peripheral arterial occlusive disease.

The purpose of the present investigation was to examine the effects of theophylline on the pharmacokinetics of pentoxifylline and one of its primary metabolites using the rat as an animal model. In addition, a semiquantitative comparison of the effects of pentoxifylline on theophylline pharmacokinetics is presented. The doses of theophylline and pentoxifylline selected in the present evaluation were selected to produce serum concentrations in the ranges observed clinically.

STUDY DESIGN

Fifteen male Sprague-Dawley rats (250 to 300 g; ACE Breeders, Boyertown, Pa.) were randomly assigned to one of three groups (five rats per group). The animals were lightly anesthetized with diethyl ether, after which time a catheter was threaded into the right atria via the right jugular vein. Drugs were administered by direct iv injection through the left jugular vein following the recovery of the animals from anesthesia. The first group of animals received a 1-mg/kg bolus of pentoxifylline alone; 5 min following the same bolus dose of pentoxifylline, the second group of rats received a 10-mg/kg bolus dose of theophylline. To permit evaluation of potential effects of pentoxifylline on theophylline pharmacokinetics, a third group of rats received a 10-mg/kg bolus dose of theophylline alone. Blood samples (approximately 0.4 ml) were obtained through the right jugular venous catheter just prior to and serially for 185 min following the last drug injection. Serum concentrations of pentoxifylline and one of its major metabolites, 3,7-dimethyl-1-(5-hydroxyhexyl)xanthine, were analyzed in samples from Groups 1 and 2 by the method of Luke and Rocci (11). Theophylline serum concentrations were determined in the samples for Groups 2 and 3 using the high-performance liquid chromatographic method of Adams *et al.* (12).

Pentoxifylline serum concentration–time data were analyzed by noncompartmental pharmacokinetic analysis employing the LAGRAN computer program (13). Statistical analysis of the pharmacokinetic data was accomplished through the use of an unpaired *t* test, which assumed that the variances in the two groups of animals being compared were unequal.

RESULTS AND DISCUSSION

Selected pharmacokinetic parameters for pentoxifylline when administered alone and in conjunction with theophylline are presented in Table I. Coadministration of theophylline had no apparent effects on the pharmacokinetics of pen-

[1] Division of Clinical Pharmacology, Jefferson Medical College, Philadelphia, Pennsylvania 19107.
[2] Division of Allergy and Clinical Immunology, Jefferson Medical College, Philadelphia, Pennsylvania 19107.
[3] Department of Pharmacy, Philadelphia College of Pharmacy and Science, Philadelphia, Pennsylvania 19104.

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Table I. Mean (±SD) Pharmacokinetic Parameters for Pentoxifylline and a Metabolite, 3,7-Dimethyl-1-(5-hydroxyhexyl)xanthine, When Administered to Rats Alone and in Conjunction with Theophylline

	Pentoxifylline (*N* = 5)	Pentoxifylline & theophylline (*N* = 5)
Pentoxifylline		
Total area under the plasma concentration vs time curve (AUC_p), ng · min/ml	13,848 (5,261)	13,448 (2,674)
Systemic clearance, ml/min	24.9 (10.3)	23.7 (5.2)
Elimination half-life, min	16.4 (13.1)	16.4 (8.9)
Volume of distribution steady state, ml	468 (135)	466 (56)
3,7-Dimethyl-1-(5-hydroxyhexyl)xanthine		
Partial area under the plasma concentration vs time curve (to 50 min) (AUC_m), ng · min/ml	2,613 (1,069)	3,038 (864)
Peak concentration, ng/ml	95 (43)	107 (37)
AUC_m/AUC_p	0.17 (0.06)	0.19 (0.06)

toxifylline or its major metabolite. The mean serum concentration–time courses of theophylline when administered alone and in conjunction with pentoxifylline are presented in Fig. 1. While a formal analysis of theophylline pharmacokinetics was not possible owing to the relatively long theophylline half-life compared to the duration of blood sampling, theophylline serum concentrations appeared lower with pentoxifylline coadministration (Fig. 1). Despite this tendency, no significant difference existed in the areas under the theophylline serum concentration–time curves measured to the last data point when the mean (SD) value obtained during pentoxifylline coadministration [1588 (150) mg min liter^{-1}] was compared to the control value [1714 (333) mg min liter^{-1}].

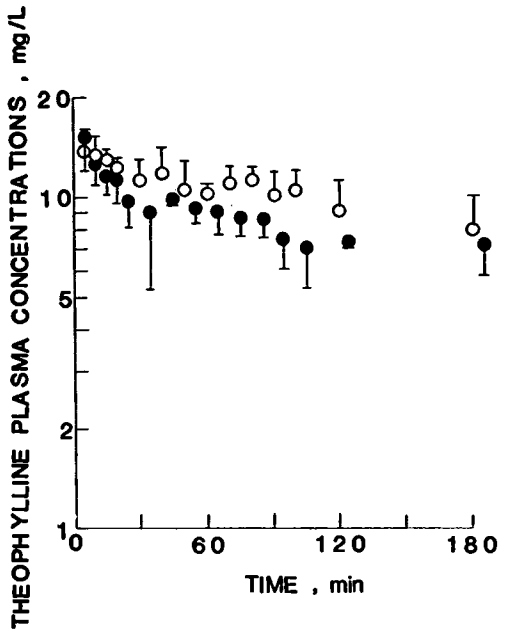

Fig. 1. Mean (±SD) plasma concentrations of theophylline when given alone (open circles) and in conjunction with pentoxifylline (filled circles) to rats.

The results of the present study suggest that theophylline does not alter the pharmacokinetics of pentoxifylline or one of its major metabolites despite the existence of similar sites for metabolism on the xanthine nucleus of each compound. In addition, based on our limited evaluation, no effects of pentoxifylline on theophylline pharmacokinetics could be discerned.

Theophylline elimination in the rat has been characterized by 49, 15, and 6.6% of an intravenous dose being excreted into the urine in 24 hr as theophylline, 1,3-dimethyluric acid, and 1-methyluric acid, respectively (14). In addition, 3.1% of the dose is excreted into feces (14). The metabolic fate of the remaining 26% of the dose is unknown. Lohmann and Miech have characterized the 8-hydroxylation of theophylline to form 1,3-dimethyluric acid as a cytochrome P_{450}-mediated reaction (15). In contrast, the formation of 1-methyluric acid has been shown to have sequential cytochrome P_{450} (3-demethylation)- and xanthine oxidase (8-hydroxylation)-mediated components (15). The species differences in the metabolic fate of theophylline between the rat and the human (see Introduction) would have limited the extrapolation to humans of any significant effects of pentoxifylline on theophylline pharmacokinetics had they occurred.

The metabolic fate of pentoxifylline in the rat is incompletely understood. Studies in our laboratories have suggested these processes to be cytochrome P_{450}-mediated reactions since the metabolism of pentoxifylline is substantially inhibited by cimetidine (16). Fujimoto *et al.* have examined the metabolism of pentoxifylline in rats following its oral administration (5). The mean urinary recovery of pentoxifylline and its metabolites over a 24-hr period was 64.4% of the dose. The major metabolites found in the urine were both stereoisomers of the 4,5-dihydro derivative as well as the

3-carboxypropyl metabolite of pentoxifylline (16). Thus, unlike theophylline, demethylation does not appear to be a major route of metabolism for pentoxifylline. Fujimoto et al. have postulated that rapid elimination of pentoxifylline metabolites prior to demethylation, steric hinderance by the oxohexyl side chain, or a combination of these factors may explain why pentoxifylline does not form a demethylated metabolite to a significant degree *in vivo* (5).

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