The Effects of Quinolones on Xanthine Pharmacokinetics

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Caffeine, theobromine, and theophylline are among the most widely consumed compounds in beverages and in pharmaceutical preparations. These methylxanthine alkaloids are metabolized by similar pathways involving demethylation and hydroxylation that are predominantly cytochrome P-450 mediated. In vivo and in vitro evidence suggests that the cytochrome P-450 isozymes involved in the demethylation pathways are distinct from the cytochrome P-450 isozymes involved in the hydroxylation pathways. Although distinctions can be made between demethylation and hydroxylation pathways, the evidence suggests that these different cytochrome P-450 isozymes are under common regulatory control. Any drug inhibiting the family of cytochrome P-450 isozymes involved in the metabolism of the methylxanthines would, therefore, be expected to have a similar effect on theophylline, theobromine, and caffeine.

A number of quinolones, including enoxacin, pipemidic acid, ciprofloxacin, norfloxacin, and pefloxacin, have been shown to reduce the clearance of theophylline, while lomefloxacin has no effect on theophylline or caffeine clearance. It has been hypothesized that only fluoroquinolones that form a 4-oxo-metabolite inhibit theophylline clearance. Lomefloxacin, which does not form a 4-oxo-metabolite, would therefore not be expected to inhibit the clearance of theophylline or caffeine. In contrast, ciprofloxacin, which does form a 4-oxo-metabolite, has been shown to reduce theophylline and caffeine clearances by about one third. Another hypothesis for the differences among quinolones suggests that quinolones that have a greater impact on theophylline clearances are more stereochemically similar to theophylline. Substitutions at position 8 on the quinolone nucleus (as in lomefloxacin) would result in stearic hindrance and decrease the structural similarity to theophylline.

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The structurally related, naturally occurring alkaloids caffeine (1,3,7-trimethylxanthine), theobromine (3,7-dimethylxanthine), and theophylline (1,3-dimethylxanthine) are among the most widely and frequently consumed compounds throughout the world. It has been estimated that the mean daily intake of caffeine in the United States from beverages is 3 mg/kg [1], and approximately 1,000 prescription drug products and 2,000 nonprescription drug products contain caffeine. Theobromine is a major constituent of cocoa and a minor constituent of tea and coffee and to a lesser extent is included in pharmaceutical preparations. Theophylline has found widespread clinical use as a bronchodilator and is a minor constituent of tea.

METHYLXANTHINE METABOLISM

The isomeric dimethylxanthine, paraxanthine (1,7-dimethylxanthine), theophylline, and theobromine are primary metabolic products of caffeine degradation. Theophylline is metabolized via 1-, 3-demethylation and 8-hydroxylation to form 3-methylxanthine, 1-methylxanthine, and 1,3-dimethyluric acid, respectively [2]. In contrast, caffeine also undergoes biotransformation involving demethylation and 8-hydroxylation pathways and is also metabolized to a uracil derivative [3]. Theobromine is similar to theophylline in that it undergoes demethylation and 8-hydroxylation reactions. Like caffeine, theobromine forms uracil derivatives via a ring open intermediate [4,5]. The naturally occurring methylxanthines are metabolized by similar primary metabolic pathways, which are cytochrome P-450 mediated.

In vivo in humans there is a high degree of correlation between the clearances of the various methylxanthines, suggesting that the isozymes involved are coregulated [6]. The individual pathways for theophylline are also highly correlated in healthy subjects [6].

In vivo data for theophylline suggest that the demethylation and 8-hydroxylation reactions are carried out, at least in part, by different cytochrome P-450 isozymes. Cigarette smoking [7] induces the demethylation pathways to a greater extent than the 8-hydroxylation pathways, and both propranolol [8] and cimetidine [9] reduce the demethylation partial clearances to a greater extent than the 8-hydroxylation clearance pathway.

In vitro evidence also confirms the distinction between the demethylation and 8-hydroxylation pathways [10]. Similarly, in the metabolism of theobromine, cigarette smoking and sulfinpyrazone pretreatment induce the 3- and 7-demethylations, which suggests that these might be mediated by different forms of cytochrome P-450 [11]. Formation of the uracil derivative is inhibited by cimetidine but induced by cigarette smoking [11] and sulfinpyrazone treatment [11], suggesting involvement of cytochrome P-450 in the formation of the uracil derivative. The oxidative metabolism of the methylxanthines appears to be carried out by a group of cytochrome P-450 isozymes under common regulatory control. Any drug inhibiting the cytochrome P-450 isozymes involved in the metabolism of the methylxanthines would be expected to have a similar effect on theophylline, theobromine, and caffeine, depending on the contribution of each pathway to the overall clearance of the parent compound.

QUINOLONE–METHYLXANTHINE INTERACTIONS

The newer fluoroquinolones, enoxacin, pefloxacin, ciprofloxacin, and ofloxacin, have all been shown to inhibit the metabolism of theophylline to varying degrees. Wijnands *et al* [12] suggested that the similarities in the chemical structure between enoxacin, ciprofloxacin, and the methyl substituted analogues pefloxacin and ofloxacin precluded the parent drug's being the cause of the inhibition of theophylline metabolism. There are differences in the metabolic clearance of these newer quinolones, especially in the formation of 4-oxo-metabolite, with ofloxacin showing only traces of the 4-oxo-metabolite.

Wijnands *et al* [12] also suggested that the inhibition of theophylline metabolism by the quinolones was due to the formation of the 4-oxo-metabolite. The evidence supporting this theory was as follows: the 4-oxo-piperidine group is chemically similar to the N^1-N^3 portion of the dimethylxanthine structure and the extent of inhibition of theophylline metabolism correlated with the urinary recovery of the 4-oxo-metabolite for enoxacin, ciprofloxacin, and pefloxacin.

Consistent with this hypothesis is the fact that nalidixic acid does not inhibit theophylline and is not metabolized to the 4-oxo-metabolite. However, there are exceptions; for example, pipemidic acid does not form a 4-oxo-metabolite but is a potent inhibitor of theophylline metabolism.

Harder *et al* [13] suggested an alternative hypothesis: that the methylxanthine interaction is coincident with the naphthyridine (enoxacin) or pyrido-pyrimidine (pipemidic acid) structure bound to a piperazine ring. Quinolones having the greatest impact on theophylline clearance are therefore more stereochemically similar to theophylline. Substitutions at position 8 on the quinolone nucleus would result in stearic hindrance and decrease the similarity in structure with theophylline.

The latter hypothesis is supported by in vitro interaction studies with caffeine [14], theophylline [15], and the quinolones that demonstrate competitive inhibition consistent with the in vivo studies. In addition, preincubation of the quinolones with human liver microsomes produced identical results, suggesting that the parent compound and not the metabolite(s) are responsible for inhibition of theophylline metabolism. In vivo and/or in vitro studies with the 4-oxo-quinolone metabolites are required to clarify which hypothesis is correct.

QUINOLONE–THEOPHYLLINE INTERACTIONS

The ability of fluoroquinolones to inhibit theophylline clearance is well documented. The magnitude of the reduction in clearance varies between the fluoroquinolones, with a 64% decrease in theophylline clearance with enoxacin [12,16] and a 30% decrease with ciprofloxacin or pefloxacin [12,17].

To identify which theophylline metabolic pathways (1-demethylation, 3-demethylation, and 8-hydroxylation) were inhibited by fluoroquinolones, a steady-state study in nine healthy volunteers was performed with ciprofloxacin [18]. In addition, lomefloxacin, a newer fluoroquinolone, which is substituted at the 8 position and which does not form a 4-oxo-metabolite, was included to test the hypothesis that the quinolones without a 4-oxo-metabolite do not inhibit theophylline metabolism.

Ciprofloxacin treatment reduced mean plasma theophylline clearance by 27%, consistent with the 30% reduction in theophylline clearance reported previously [12,17]. Clearance by all three metabolic pathways was reduced, although the reduction via the 8-hydroxylation pathway (24%) was less than the reduction via the 1-demethylation (37%) and 3-demethylation (42%) pathways (**Figure 1**). The difference in reduction of clearance via the 8-hydroxylation pathway was not statistically significant ($p > 0.05$) from the reduction in clearance via the 1-demethylation and 3-demethylation pathways.

Lomefloxacin treatment had no effect on theophylline metabolism, consistent with the hypothesis that it is the 4-oxo-metabolites of the fluoroquinolones that inhibit theophylline metabolism [12]. Lomefloxacin, unlike ciprofloxacin, does not form a 4-oxo-metabolite. In addition, as lomefloxacin is substituted in the 8 position, the lack of interaction could also be consistent with the alternative hy-

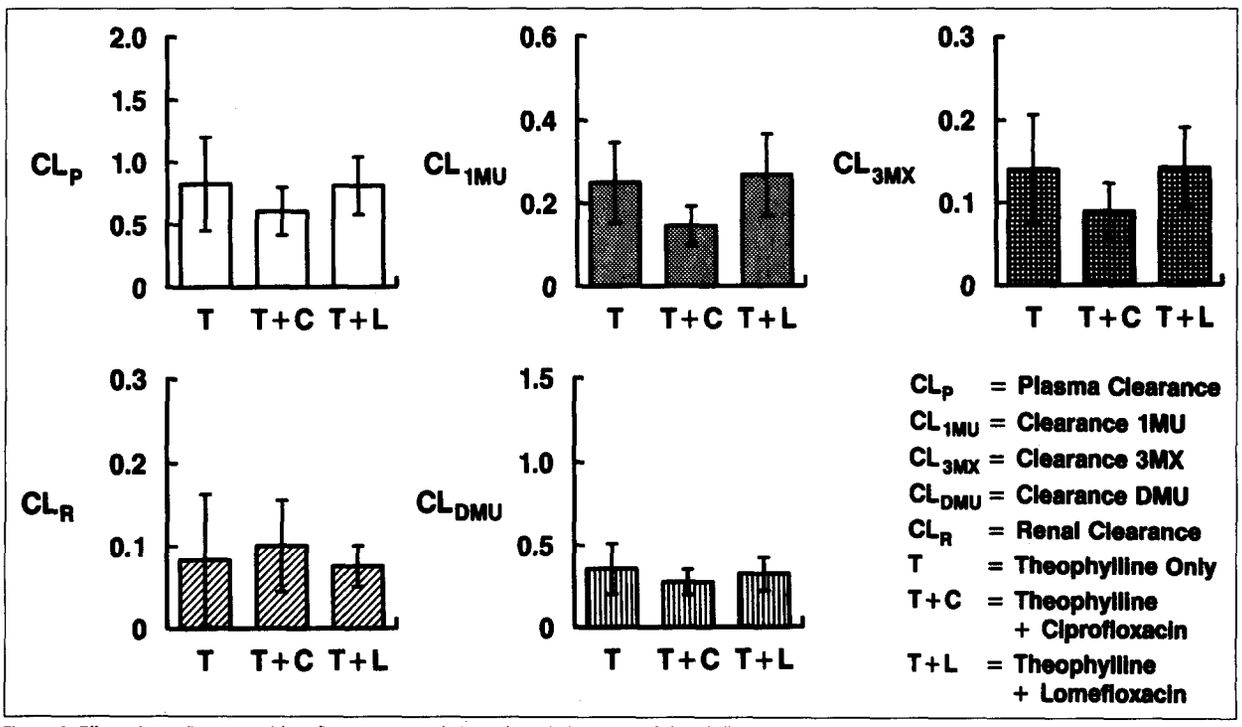

Figure 1. Effect of ciprofloxacin and lomefloxacin on metabolic and renal clearances of theophylline.

pothesis that the parent compound is responsible for the inhibition of theophylline metabolism.

The quinolone–theophylline interactions are summarized in **Table I.** The data suggest that the reduction in theophylline clearance by enoxacin, ciprofloxacin, pefloxacin, ofloxacin, and pipemidic acid are of clinical importance.

TABLE I

Summary of Quinolone–Theophylline/Caffeine Interactions

Quinolone	Total Daily Dose (mg)	Percentage Inhibition	
		Theophylline	Caffeine
Enoxacin	200	—	58% [13]
	400	—	64% [13]
	800	64% [12]	78% [13,19]
		74% [20]	
Pipemidic acid	800	50% [21]	65% [13]
			63% [22]
Ciprofloxacin	200	—	No effect [13]
	500	—	37% [13]
			33% [19]
	1,000	30% [12]	37% [13]
	1,500	30% [23]	37% [13]
Norfloxacin	800	10% [24]	No effect [13]
		15% [25]	
	1,600	—	35% [22]
Pefloxacin	800	29% [12]	—
Ofloxacin	400	No effect [26]	No effect [13,19]
	800	10% [27]	
Lomefloxacin	400	No effect [21,28]	No effect [29]
	800	No effect [18,29]	

QUINOLONE–CAFFEINE INTERACTIONS

Caffeine is metabolized, similarly to theophylline, by primary metabolic pathways that are cytochrome P-450 mediated. As discussed, any drug inhibiting the cytochrome P-450 isozymes involved in theophylline metabolism would be expected to affect caffeine metabolism similarly. The quinolone–caffeine interaction studies are summarized in Table I.

Lomefloxacin does not inhibit theophylline or caffeine. A double-blind, two-way crossover, steady-state study by Healy *et al* [29], in which 16 healthy volunteers received either lomefloxacin 400 mg daily or placebo with caffeine 200 mg daily for 5 days, confirmed that lomefloxacin did not alter the disposition of caffeine.

In contrast, ciprofloxacin [30] inhibited caffeine by 33%. The reduction in caffeine clearance was accompanied by 43% reduction in the appearance of paraxanthine, the major metabolite, suggesting that the reduction in caffeine clearance is due to inhibition of the cytochrome P-450 isozyme involved.

CONCLUSION

Although the exact mechanism by which the quinolones inhibit methylxanthine metabolism is yet to be clarified, the pattern of quinolone inhibition is consistent between theophylline and caffeine.

Clinically, the quinolone–theophylline interactions are important because of the low therapeutic index of theophylline; a reduction in the dosage of theophylline is required when certain quinolones (enoxacin, pipemidic acid, ciprofloxacin, norfloxacin, and pefloxacin) are coadministered. The quinolone–caffeine interaction may result in unexpected effects, for example, tachyarrhythmia, central agitation, and nausea following caffeine intake.

Lomefloxacin, which does not inhibit theophylline or caffeine, can be safely coadministered with methylxanthines.

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