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The influence of quinolone derivatives on theophylline clearance

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1 Enoxacin decreases the metabolic clearance of the bronchodilator theophylline not only in severely ill patients, but also in patients with stable chronic obstructive airways disease.
2 In this comparative study, significantly increased plasma theophylline concentrations were measured during co-administration of enoxacin (110.9%) and, to a lesser degree, also during co-administration of pefloxacin (19.6%) and ciprofloxacin (22.8%).
3 Total body clearance of theophylline was significantly decreased by enoxacin (63.6%), ciprofloxacin (30.4%) and pefloxacin (29.4%). The pharmacokinetic parameters of theophylline did not change during co-administration of ofloxacin and nalidixic acid.
4 There is growing evidence that the observed interaction is caused not by the parent drugs, but by the 4-oxo metabolite of enoxacin, pefloxacin and ciprofloxacin.

Keywords quinolone 4-oxo quinolone enoxacin pefloxacin ciprofloxacin ofloxacin nalidixic acid theophylline interaction lower respiratory tract infections

Introduction

During two different clinical studies in patients with chronic obstructive lung disease (COLD), testing the efficacy and safety of enoxacin (CI 919), a new antibacterial agent of the quinolone class, unexpectedly high plasma theophylline concentrations were measured in patients who were on concomitant theophylline therapy. These high theophylline concentrations resulted in severe complaints of nausea, vomiting, tachycardia or agitation for some of the patients (Wijnands *et al.*, 1984; Davies *et al.*, 1984). Further investigation into this increase in plasma theophylline concentrations showed that neither theophylline protein binding nor theophylline renal clearance were influenced by the enoxacin co-medication; it was therefore concluded that the interaction mechanism might be a decreased theophylline metabolic clearance (Wijnands *et al.*, 1985b).

Due to the clinical importance of this observed interaction between enoxacin and theophylline, other new quinolones which are currently being clinically tested to treat respiratory tract infections were studied to see if they produced a similar interaction.

Methods

Subjects and materials

Eight subjects, seven males and one female, aged 51 to 69 years (mean age: 58.5 ± 6.2 years) gave their informed consent to be included in this study, which had the approval of the hospital ethics committee. All eight patients were on maintenance theophylline treatment (Theolin retard, Astra Pharmaceutics) due to COLD, which was stable for at least 4 weeks prior to the measurement period. The theophylline dose was 300 mg twice daily in five cases, 450 mg twice daily in one case and 600 mg twice daily in two

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cases. In all cases, for safety reasons, trough plasma theophylline concentrations were kept below 10 $\mu g\ ml^{-1}$. At the time of the study the patients used only sympathomimetics and cortico steroids by inhalation as co-medication, drugs which are known not to influence theophylline clearance. None of the patients showed signs of congestive heart failure. Seven subjects did not smoke. One smoked approximately five cigarettes a day; he was asked not to change his smoking habit during the study period. Before the start of the study a medical history, physical examination, complete blood count, blood chemistry and a urinalysis were performed; the results were within normal ranges for each subject.

All subjects participated in five study periods, each separated by at least 9 days: theophylline alone (= blank period), theophylline with ciprofloxacin 500 mg twice daily, theophylline with pefloxacin 400 mg twice daily, theophylline with ofloxacin 400 mg twice daily, and theophylline with enoxacin 400 mg twice daily. After completion of these measurements a sixth period of theophylline and nalidixic acid 500 mg twice daily was added in four of these subjects. After steady-state theophylline plasma concentrations (C_{ss}) were confirmed (difference of 2 $\mu g\ ml^{-1}$ or less between two measurements on 2 consecutive days), the quinolone administration was started; the tablets were ingested together with the theophylline at 09.00 h and 21.00 h for a 5.5 day period (last quinolone administration: day 6 at 09.00 h). On day 5 of the quinolone administration after the morning dose or when plasma theophylline concentrations exceeded 20 $\mu g\ ml^{-1}$, theophylline was stopped for at least 32 h or until the plasma theophylline concentration was less than 1 $\mu g\ ml^{-1}$. Adverse reactions were registered by the volunteers.

Sampling procedure

Blood samples were taken at 08.30 h on day 2, 3, 4 and 5 of each period to determine trough plasma theophylline concentrations. On day 5 and 6 serial blood samples were taken from an indwelling catheter in a forearm vein, which was kept open by a heparin solution, to establish theophylline plasma concentration-time curves for each subject, up to 48 h after the last theophylline dose or until plasma theophylline concentration was less than 1 $\mu g\ ml^{-1}$. Plasma was separated immediately. All samples of spontaneously voided urine were collected for a 24 h period. Plasma and urine samples were kept at −20° C pending analysis.

Sample analysis

Theophylline plasma and urine concentrations were determined by a homogenous enzyme immunoassay technique (EMIT; Syva Diagnostics, Palo Alto, California, USA) (Gushaw *et al.*, 1977), using a Gilford Stasar III spectrophotometer, wave length 340 nm. A lyophilized assayed human control serum was used (Lyphochek, Boi Rad, California, USA). This technique is known to correlate significantly with high pressure liquid chromatography analysis (Koup & Brodsky, 1978). Urine samples were diluted six times. To exclude the possibility of influence by the quinolones on the EMIT analysis of theophylline, selected plasma samples were measured by both h.p.l.c. and EMIT: the theophylline concentrations appeared to be identical.

Quinolone plasma concentrations and the 4-oxo metabolite (formed with ciprofloxacin, pefloxacin and enoxacin) were determined by a h.p.l.c. method (Vree *et al.*, 1985): A Spectra Physics 3500B high performance liquid chromatograph equipped with a stainless steel, reversed phase column 15 cm, 4 mm i.d., packed with Spherisorb 5 ODS (Chrompack, Middelburg, The Netherlands) and a variable wave length spectrophotometer detector (model SP 770) were used. The mobile phase consisted of a mixture of 0.75 g phosphoric acid, 0.25 g tetramethylammoniumchloride, 155 ml *N*,*N*-dimethylformamide and 155 ml acetonitrile, adjusted with water to 1 l. The chemicals were of analytical grade (Merck, Darmstadt, F.R.G.). Solvent flow rate was 1.6 ml min^{-1} at a pressure of 3800 psi.

The following parameters of theophylline were recorded i.e. calculated for each study period: C_{max}, C_{min}, area under the plasma concentration-time curve after oral administration (AUC $0-\infty$), total body clearance after oral administration (CL), renal clearance (CL_r) and the apparent half-life of elimination. AUC($o-\infty$) was calculated by the linear trapezoidal rule. CL of theophylline was obtained by dividing the dose by the AUC in the 12 h period. The half-life of theophylline was deduced from linear least squares regression analysis of semilogarythmic experimental data points in the terminal part of the concentration-time curve. These calculations assumed that the dose of theophylline was completely absorbed, as has been shown in several studies (Hendeles *et al.*, 1977).

Results are expressed as mean values ± standard deviation. Differences in the parameters between the periods in which theophylline with one of the quinolones was administered and the blank period were assessed using Student's *t*-test

for paired observations; differences were considered significant at the $P < 0.05$ level.

Results

Mean trough theophylline concentrations prior to the five different study periods did not differ significantly (Table 1). Mean trough theophylline concentrations on day 2, 3, 4 and 5 of the measurement periods are shown in Figure 1.

During enoxacin administration a significant raise of theophylline concentrations occurred on the second day of enoxacin administration in all subjects compared to the blank period ($P < 0.001$). In two subjects on enoxacin, theophylline had to be discontinued on day 3 and day 4 respectively because theophylline plasma concentrations exceeded 20 $\mu g\,ml^{-1}$, and there were moderately severe complaints of agitation, restlessness and nausea. After the third day of administration, no further increase in the theophylline concentration was observed.

During co-administration with ciprofloxacin and pefloxacin, a significant increase of theophylline plasma concentrations occurred on day 3 of administration ($P < 0.001$). On the contrary, no change in theophylline plasma concentrations was observed during co-administration with ofloxacin.

A highly significant rise of maximum theophylline plasma concentrations occurred during co-administration of enoxacin ($P < 0.001$), ciprofloxacin and pefloxacin ($P < 0.05$); trough theophylline plasma concentrations were raised during co-administration of enoxacin ($P < 0.001$), and to a lesser degree, during pefloxacin and ciprofloxacin co-administration ($P < 0.05$). Mean AUC values increased during enoxacin ($P < 0.001$) and pefloxacin and ciprofloxacin administration ($P < 0.01$). No change in these parameters was measured during ofloxacin administration. A significant increase in the theophylline half-life was seen during the co-administration of enoxacin ($P < 0.001$), pefloxacin ($P < 0.01$) and ciprofloxacin ($P < 0.01$). Total body clearance of theophylline decreased 63.6% during enoxacin co-administration ($P < 0.01$), 29.4% during pefloxacin co-administration and 30.4% during ciprofloxacin co-administration (both $P < 0.05$). No change in the renal clearance occurred during co-administration of the different quinolones when compared to the blank period. During ofloxacin co-medication no change in the theophylline half-life or total body clearance was measured.

After completion of these five study periods, a sixth period was added in four of these subjects

Table 1 Some pharmacokinetic parameters of theophylline when ingested alone (blank), or during comedication with enoxacin, pefloxacin, ciprofloxacin, ofloxacin ($n = 8$) or nalidixic acid ($n = 4$) (mean ± s.d.).

	C_{ss} ($\mu g\,ml^{-1}$)	C_{max} ($\mu g\,ml^{-1}$)	C_{min} ($\mu g\,ml^{-1}$)	AUC_o^∞ ($mg\,l^{-1}\,h$)	$t_{½}$ (h)	CL ($ml\,min^{-1}$)	CL_r ($ml\,min^{-1}$)
Blank	6.1 (2.1)	9.2 (1.8)	6.3 (2.4)	146 (67)	5.9 (2.5)	85.9 (33.4)	7.6 (1.5)
Enoxacin	6.3 (2.0)	19.4 (2.8)***	16.6 (2.5)***	537 (125)***	15.3 (5.3)***	31.3 (7.8)**	7.2 (1.8)
Pefloxacin	5.7 (1.8)	11.0 (1.8)*	8.6 (2.6)***	224 (79)**	8.6 (3.6)**	60.6 (23.8)*	7.5 (1.7)
Ciprofloxacin	5.3 (1.7)	11.3 (2.6)*	8.8 (3.1)***	222 (100)**	8.4 (2.4)**	59.8 (27.4)*	7.0 (1.6)
Ofloxacin	6.2 (1.9)	8.5 (2.1)	6.3 (2.3)	147 (60)	6.0 (2.1)	81.5 (31.1)	6.6 (1.0)
Nalidixic acid	6.3 (1.9)	9.1 (1.8)	6.6 (1.6)	138 (48)	5.7 (2.3)	82.4 (15.9)	8.0 (2.7)

C_{ss} = trough theophylline plasma concentration before the administration of the quinolone; C_{max} = maximum theophylline plasma concentration; C_{min} = trough theophylline plasma concentration AUC_o^∞ = area under the concentration-time curve of theophylline; $t_{½}$ = observed half-life of theophylline; CL = total body clearance; CL_r = renal clearance.
*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$

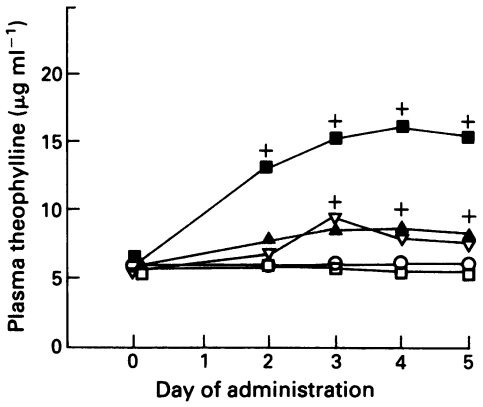

Figure 1 Mean trough plasma theophylline concentrations in subjects when given alone (= blank, ○), or during co-administration with ofloxacin (□), pefloxacin (▽), ciprofloxacin (▲) and enoxacin (■) (+ $P < 0.001$).

following the same study design, in which nalidixic acid, 500 mg twice daily was co-administered. The theophylline parameters did not change when compared to the blank period (Table 1).

No correlation could be found between the change in the theophylline AUC values or the apparent elimination half-life and the AUC values of the parent quinolone. Of the enoxacin dose, 14.7 ± 3.6% was recovered in the urine as 4-oxo metabolite; of ciprofloxacin and pefloxacin the urinary recoveries of the 4-oxo metabolite were 4.3 ± 0.9%, and 6.4 ± 1.3% respectively. There was a correlation between the urine recovery of the 4-oxo metabolite (% dose) and the increase of theophylline AUC values ($r = 0.90$) (Figure 2). No 4-oxo metabolite could be found in the urine after administration of nalidixic acid and only traces after ofloxacin.

Adverse reactions

One subject developed complaints of sleeplessness during administration of both ofloxacin and ciprofloxacin. Another subject felt depressed and had complaints of nausea and diarrhea during ofloxacin, ciprofloxacin and enoxacin administration. One subject had moderate upper abdominal complaints on day 4 and 5 of enoxacin ingestion. One other subject felt languid during the whole period of pefloxacin administration. As stated above, two subjects developed complaints during the co-administration of enoxacin and theophylline, probably related to the high theophylline plasma concentrations.

Discussion

Infections of the lower respiratory tract occur frequently in patients with COLD. Recently a group of new antibacterial agents of the quino-

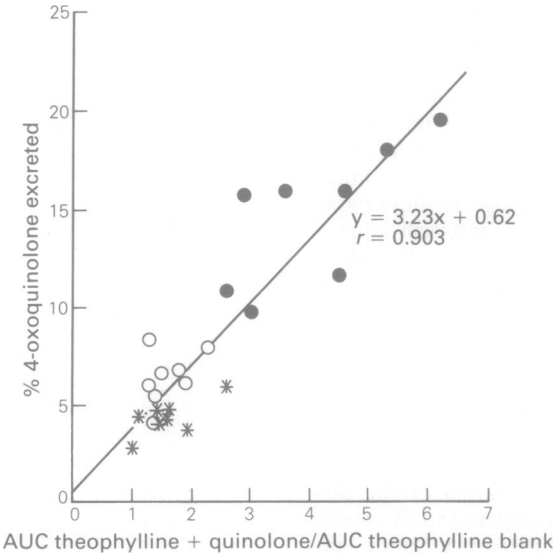

Figure 2 The increase of the AUC value for theophylline during co-medication with enoxacin (●), ciprofloxacin (*) or pefloxacin (○) compared to the blank AUC, *vs* the urinary excretion in 24 h of 4-oxo quinolone, expressed as % of the ingested dose.

lone class has been developed. Some of these agents, such as ciprofloxacin, ofloxacin, perfloxacin and enoxacin share a good *in vitro* activity on both Gram positive and Gram negative bacteria, including multiresistant *Pseudomonas aeruginosa* strains, and show a good penetration into bronchial secretions and lung tissue after oral dosing (Bergogne-Berezin, 1985).

A large elevation of theophylline plasma concentrations was reported during concomitant treatment with enoxacin in patients, who were hospitalized due to an exacerbation in their pulmonary disease. In some of these patients, this interaction gave rise to signs and symptoms of theophylline toxicity (Davies *et al.*, 1984; Wijnands *et al.*, 1985a). The present study confirms this interaction in subjects with stable pulmonary disease, whose only simultaneous treatment is with sympathomimetics and corticosteroids, by inhalation.

In spite of the fact that during concomitant treatment of theophylline with ciprofloxacin, pefloxacin or ofloxacin no clinical signs of theophylline toxicity were reported in earlier clinical reports (Davies *et al.*, 1986), this study demonstrates that ciprofloxacin and pefloxacin also influence theophylline clearance. The magnitude of this interaction is significantly smaller than the effect of enoxacin. Nevertheless, because of the considerable interindividual difference in the size of the effect on theophylline clearance, the influence of ciprofloxacin and pefloxacin can be expected to be of clinical importance in a proportion of the patients. Recently, Raoof and co-workers reported in 60% of patients on concomitant treatment with theophylline and

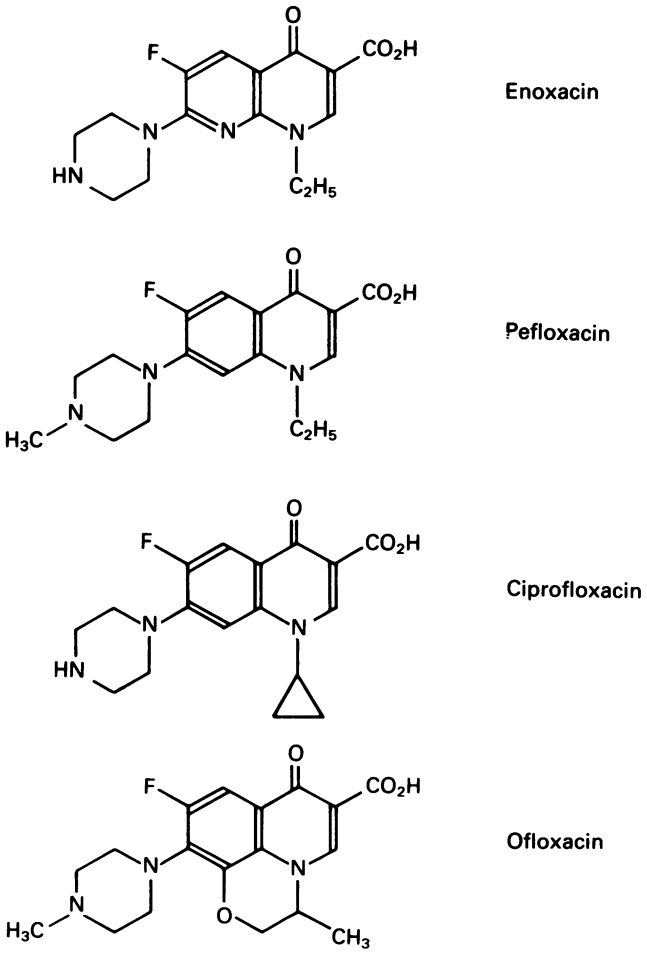

Figure 3 Chemical structures of enoxacin, pefloxacin, ciprofloxacin and ofloxacin.

ciprofloxacin 750 mg twice daily, a significant increase of theophylline plasma concentrations from 7.9 ± 4.8 μg ml^{-1} to 18.4 ± 6.5 μg ml^{-1} (Raoof *et al.*, 1985). A possible interaction between ciprofloxacin and theophylline was also reported by Scully & Neu (1985). In both studies the ciprofloxacin dose was higher than the dose used in this study.

The similarities in chemical structure between enoxacin, ciprofloxacin and the *N*-methylsubstituted analogues pefloxacin and ofloxacin (Figure 3) preclude the structure of the parent drug being the cause of the interference with the theophylline clearance. However, there are differences in the metabolic clearance of these four quinolones, especially in the formation of 4-oxo quinolone: ofloxacin showed only traces of a 4-oxo metabolite. Nalidixic acid, the oldest quinolone, is metabolized into hydroxy- and carboxynalidixic acid without forming a 4-oxo metabolite: the pharmacokinetic parameters of theophylline in four subjects on nalidixic acid did not differ from those of the blank period.

A correlation was found between the extent of the interaction and the urinary recovery of the 4-oxo metabolite. The 4-oxo group seems therefore to be responsible for the interaction with the theophylline clearance. The 4-oxo piperidine group shows a chemical structure similar to the N1-N3 part of the dimethylxanthine structure.

Cimetidine, a drug known to inhibit the demethylation processes and which has also a strong effect on theophylline clearance has a similar stucture in the imidazole group. Grygiel *et al.* (1984) showed that during co-administration with cimetidine, theophylline clearance diminished largely due to reduced *N*-demethylation. It is possible that the above mentioned part of the molecule, found in cimetidine and in 4-oxo quinolone, competes with theophylline for liver enzymes (Figure 4).

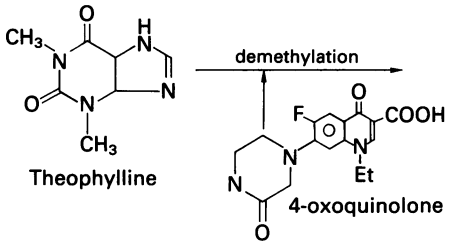

Figure 4 Proposed mechanism of the influence of 4-oxo quinolone on the metabolic degradation of theophylline.

If simultaneous administration of theophylline and enoxacin is necessary, it is recommended to halve the theophylline dose before starting enoxacin and to monitor theophylline plasma concentrations daily during the treatment to avoid toxicity. In the case of ciprofloxacin and pefloxacin co-medication, the theophylline dose needs no pretreatment adjustment but measurements of theophylline plasma concentrations during treatment are essential, especially in patients who develop adverse reactions. In the present study no effect was measured during ofloxacin administration.

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