Enoxacin decreases the clearance of theophylline in man

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1 In patients treated concurrently with theophylline and enoxacin, a new broad-spectrum antibacterial agent of the quinolone class, unexpectedly high plasma theophylline concentrations were measured.

2 In part I of this study, daily plasma theophylline concentrations were measured in 14 patients. The mean $\pm$ s.d. theophylline concentrations increased from $8.5 \pm 2.8 \mu\text{g ml}^{-1}$ prior to enoxacin to a maximum of $21.7 \pm 7.8 \mu\text{g ml}^{-1}$ during coadministration.

3 In part II, six of these patients received aminophylline intravenously at a constant infusion rate and under controlled conditions. Plasma theophylline concentrations rose from $8.4 \pm 2.4 \mu\text{g ml}^{-1}$ prior to enoxacin treatment to $15.0 \pm 5.1 \mu\text{g ml}^{-1}$ at day 3 of coadministration ($P < 0.005$).

4 Plasma protein-binding and renal clearance of theophylline remained unchanged, whereas total body clearance of theophylline significantly decreased ($P < 0.005$).

5 From these observations it is concluded that the rise of plasma theophylline concentrations is caused by a reduced metabolic clearance of theophylline.

6 If concomitant use of both drugs is necessary, monitoring of plasma theophylline concentration and adjustment of the theophylline dose is recommended.

Keywords quinolone enoxacin theophylline interaction
lower respiratory tract infections

Introduction

Theophylline is a potent bronchodilator and is frequently prescribed for the treatment of patients with obstructive lung disease. The bronchodilatory effect of theophylline is related to its plasma concentration with an optimal therapeutic effect occurring at plasma concentrations of $10\text{--}20 \mu\text{g ml}^{-1}$ (Mitenko & Ogilvie, 1973). Because of this narrow therapeutic range a change in theophylline clearance will have consequences for adequate treatment. At higher plasma concentrations adverse reactions are mainly associated with the digestive, circulatory and nervous systems.

Many factors are known to influence theophyl-

line clearance (Hendeles & Weinberger, 1983). Simultaneous treatment with drugs such as allopurinol (Manfredi & Vesell, 1981), cimetidine (Jackson *et al.*, 1981; Reitberg *et al.*, 1981), erythromycin (Prince *et al.*, 1981), troleandomycin (Weinberger *et al.*, 1977), can cause decreased theophylline clearance, whereas coadministration of phenobarbitone (Landay *et al.*, 1978), phenytoin (Marquis *et al.*, 1982) and isoprenaline (Hemstreet *et al.*, 1982) can produce an increased clearance.

Recently a number of new quinolone carboxylic acid derivatives have been developed. Enoxacin, one of these new quinolones, has

shown a good *in vitro* activity against Gram-positive and Gram-negative bacteria, including *Pseudomonas aeruginosa*.

In a previous study with enoxacin in respiratory tract infections by Davies *et al.* (1984), the drug had to be discontinued in 9 of 15 patients because of side effects mainly related to the digestive system; seven of these patients used concomitant theophylline medication. In a clinical study with oral enoxacin in patients with a respiratory tract infection we observed unexpectedly high plasma theophylline concentrations causing complaints and symptoms of theophylline toxicity such as nausea and vomiting (Wijnands *et al.*, 1984). Since theophylline and antibiotics are frequently used concomitantly in the treatment of patients with obstructive lung disease, this study was designed to elucidate the mechanism of interaction between these two compounds.

Methods

Patients with chronic obstructive pulmonary disease, who were admitted to the hospital for treatment of respiratory tract infection, participated in the study, which had received the approval of the Hospital Ethics Committee. All patients were on maintenance treatment with a slow release theophylline administered twice daily. Drugs known to influence theophylline clearance were avoided prior to the study and during administration of enoxacin (Hendeles & Weinberger, 1983; Jonkman & Upton, 1984). Infections caused by *Pseudomonas aeruginosa* were treated with oral enoxacin, 600 mg twice daily, whereas other infections were treated with 400 mg enoxacin, twice daily. Patient characteristics and comedication are listed in Table 1. None of the patients had signs of congestive heart failure, nor did they smoke cigarettes or drink coffee. Hepatic and kidney functions were within normal ranges.

In part I of the study daily trough plasma theophylline concentrations were measured before the start of and during treatment with enoxacin. Plasma samples were taken at the same time of the day (09.00 h). In part II aminophylline (theophylline content 80%) was administered intravenously via an infusion pump, to obtain a constant infusion rate. After steady-state plasma theophylline concentrations were attained, i.e. difference between through concentrations on 2 consecutive days less than 2 µg ml⁻¹, oral enoxacin was started at a dose of 400 or 600 mg twice daily. Complaints occurring during enoxacin treatment were recorded in a diary.

On the day before the start of enoxacin treatment and on day 3 of coadministration serial blood samples were collected from a vein in the arm opposite that of the aminophylline infusion. Plasma was separated immediately. Specimens of spontaneously voided urine were collected over a 24 h period to assess renal clearance. Urine and plasma samples were stored at -18°C until analysis. Theophylline concentrations in plasma and urine were determined by means of an enzyme immunoassay (EMIT®, Syva Diagnostics, Palo Alto) (Gushaw *et al.*, 1977), which is known to correlate significantly with high pressure liquid chromatography (Koup & Brodsky, 1978). Protein binding was measured by ultrafiltration (EMIT®, Free Level System I, Syva Diagnostics, Palo Alto). Total body clearance of theophylline was calculated as $\text{Dose}/\tau \cdot C_{ss}$.

Results are presented as means ± s.d. Statistical analysis was performed using Student's *t*-test for paired observations; differences were considered significant at the $P < 0.05$ level.

Results

Fourteen patients (nine men and five women) with a mean age of 63.2 years (range 41–86 years) entered the study.

Part I

Mean plasma theophylline concentrations were 8.5 ± 2.8 µg ml⁻¹ prior to administration of enoxacin and increased to a highest value of 21.7 ± 7.8 µg ml⁻¹, following 3–5 days of concomitant oral enoxacin. In eight patients treated with a daily dose of 800 mg enoxacin plasma theophylline concentrations increased from 8.3 ± 3.5 µg ml⁻¹ to 21.3 ± 9.5 µg ml⁻¹ during treatment with enoxacin. In six patients treated with a daily dose of 1200 mg enoxacin, plasma theophylline concentrations increased from 8.8 ± 1.6 µg ml⁻¹ to 22.2 ± 5.5 µg ml⁻¹ during enoxacin treatment. An example of the course of plasma theophylline concentrations is given in Figure 1 for a single patient (number 4) before, during and after coadministration of enoxacin. Similar trends were observed in the other patients. In one patient (number 12) theophylline was discontinued on two occasions. On the first occasion the patient received concomitant enoxacin and on the second occasion theophylline alone. As illustrated in Figure 2 the theophylline half-life increased to 16.5 h with coadministration of enoxacin, compared to a 5.5 h half-life of theophylline when given alone.

Table 1 Patient characteristics

Patient	Age (years)	Weight (kg)	Theophylline dose (mg 24 h ⁻¹)	Enoxacin dose (mg 24 h ⁻¹)	Theophylline concentration before enoxacin	Theophylline concentration (µg ml ⁻¹) during enoxacin	Further comedication
1	64	67.7	600	800	7.0	26.6	S P Pr
2	41	51.6	816	800	12.3	20.0	S P C Pr
3	69	62.5	1200	800	9.0	17.2	S P F D
4	66	41.8	612	800	12.8	21.0	S P I R
5	56	59.0	612	800	6.5	13.6	S P
6	75	69.6	400	800	2.5	10.2	S T P
7	86	56.8	400	800	10.5	20.6	S B F D
8	76	49.0	408	800	6.1	41.3	S P
Mean: 66.6							
s.d.: 13.7							
9	61	77.6	612	1200	8.6	15.0	S P
10	69	81.5	816	1200	11.5	31.0	S T P F
11	41	60.1	612	1200	8.5	20.3	S P D F
12	54	61.0	612	1200	7.8	25.2	S P I Pm
13	75	51.7	612	1200	9.4	22.9	S P
14	52	77.5	600	1200	6.7	18.9	--
Mean: 58.7							
s.d.: 12.3							

S = salbutamol, inhalation T = terbutaline, oral P = prednisolone, i.v./oral B = beclomethasone, inhalation I = ipratropium, inhalation C = cromolyn sodium, inhalation F = frusemide, oral D = digoxin, oral Pr = prochlorperazine, oral Pm = promethazine, oral R = ranitidine, oral

Figure 1 Plasma theophylline concentration in a single patient, before, during and after coadministration of enoxacin.

Part II

In this part of the study five patients (numbers 4, 5, 9, 11, 12) received 720 mg aminophylline 24 h^{-1} intravenously (equivalent to 612 mg theophylline) and one patient (number 8) 480 mg aminophylline 24 h^{-1} (equivalent to 408 mg theophylline) (Table 1). The mean steady state plasma theophylline concentration of $8.4 \pm 2.4\text{ }\mu\text{g ml}^{-1}$, measured before starting enoxacin, increased to $15.0 \pm 5.1\text{ }\mu\text{g ml}^{-1}$ at day 3 of enoxacin treatment ($P < 0.005$, Figure 3a). Plasma protein binding of theophylline was $61.8 \pm 9.0\%$ before and $63.2 \pm 4.9\%$ following enoxacin therapy ($P > 0.05$, Figure 3b).

Total plasma theophylline clearance decreased from $50.2 \pm 10.6\text{ ml min}^{-1}$ to $28.9 \pm 7.8\text{ ml min}^{-1}$ ($P < 0.005$, Figure 3c). Renal clearance of theophylline was $7.2 \pm 4.3\text{ ml min}^{-1}$ before and $7.0 \pm 3.8\text{ ml min}^{-1}$ at day 3 of concomitant treatment ($P > 0.05$, Figure 3d). Enoxacin did not interfere with the theophylline EMIT® assay. Concentrations of selected samples measured by h.p.l.c. were equivalent to those determined by EMIT®.

Discussion

Enoxacin markedly inhibits the total body clearance of theophylline. Mean plasma theophylline concentration increased by a factor 2.6, following concomitant enoxacin administration in this study. The increase in plasma theophylline concentration appeared to be independent of enoxacin dose ($800\text{--}1200\text{ mg day}^{-1}$).

Davies *et al.* (1984) used oral enoxacin 600 mg twice daily to treat 15 patients with a lower respiratory tract infection. In nine cases enoxacin

Figure 2 Elimination of theophylline in a single patient during enoxacin treatment (○) and 1 week after enoxacin had been stopped (●).

had to be discontinued because of adverse reactions. Of these nine patients, seven who developed severe nausea, were on concomitant theophylline therapy. Plasma theophylline concentrations were not measured in that study. In the present study nine patients simultaneously treated with theophylline and enoxacin, complained of nausea and vomiting. These complaints disappeared completely and quickly after the theophylline dose was lowered, while enoxacin administration continued. Thus, the symptoms appeared to be related primarily to high plasma theophylline concentrations, rather than to any direct effect of enoxacin.

To investigate the mechanism by which enoxacin decreases theophylline clearance, aminophylline was administered by constant i.v. infusion to six patients. A clear and consistent rise in the plasma theophylline concentrations was observed in all patients following concomitant administration of enoxacin. Since the plasma protein binding and renal clearance of theophylline did not change, the decrease in theophylline clearance probably relates to effects on the liver enzymes or a change in volume of distribution.

The prolonged half-life of theophylline measured in a single patient during coadministration of enoxacin (Figure 2) suggests that a metabolic inhibition is more likely than an effect on volume of distribution.

Theophylline is primarily eliminated via hepatic metabolism (Ogilvie, 1978; Pfeifer *et al.*, 1979). Few studies have investigated the effects of drugs on the individual pathways of theophylline metabolism, *N*-demethylation and 8-oxidation. Lohman & Miech (1976) showed that the *N*-demethylation in rats is related to the hepatic

Figure 3 (a) Plasma concentration, (b) protein binding, (c) total body clearance and (d) renal clearance of theophylline before and at day 3 of concomitant treatment with enoxacin (----, mean) (NS = $P > 0.05$)

cytochrome P-448, which can be stimulated by phenobarbital (Landay *et al.*, 1978). Grygiel *et al.* (1984) showed that theophylline clearance diminished during coadministration of cimetidine largely due to reduced *N*-demethylation. Cimetidine did not influence theophylline oxidation.

The mean age of the patients in this study was 63.2 years. All but one of the patients necessarily received other comedication as indicated in Table 1. Although no influence is known from the comedication used on theophylline clearance, the interaction studied between enoxacin and theophylline needs confirmation in subjects, without further comedication. In our opinion other antibacterial agents of the quinolone class

have to be investigated with respect to this interaction because of the close chemical structure similarities to enoxacin.

Our preliminary clinical experience indicates that enoxacin may be of value in respiratory medicine as an antibacterial agent for selected indications, including Gram-negative infections. If simultaneous treatment with theophylline is necessary, we recommend lowering the theophylline dosage by approximately 40% before the start of enoxacin. Any further modification of the theophylline dosage during enoxacin treatment has to be based on measurements of plasma theophylline concentrations in order to avoid toxicity.

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