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Drug Interaction between Theophylline and New Quinolone Antibiotics*

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Theophylline is a potent bronchodilator and is widely used in the treatment of patients with obstructive airway diseases. The bronchodilatory effect of theophylline is related to its plasma concentration with an optimal therapeutic effect occuring at plasma concentrations of 10-20 μg/ml[1]. In the case of asthma accompanied with purulent respiratory infections such as pneumonia, theophylline and new quinolone antibiotics (new quinolones) are often given simultaneously. Enoxacin, one of new quinolones, decreases the clearance of theophylline and increases the blood concentration[2-4]. Consequently, the adverse reactions of theophylline are caused.

The purpose of the present study was to investigate the effects of several new quinolones on the blood concentration of theophylline in rabbits.

Methods and Materials

Male rabbits (body weight 2.5-3.0 kg) were used forming a group of 4 animals. Animals were abstained from food 24 hr before the administration of drugs.

In the control group, theophylline (Neophyllin, Eisai Pharmaceutical Co.) alone was administered orally at doses of 20 mg/kg/day, by one shot or for 4 consecutive days.

In the new quinolone treated group, theophylline and one of the new quinolones were administered orally at the same time.

New quinolones used were enoxacin (Flumark, Dainippon Pharmaceutical Co.), ciprofloxacin hydrochloride (Ciproxan,Bayer Pharmaceutical Co.), ofloxacin (Tarivid, Daiichi Pharmaceutical Co.), norfloxacin (Baccidal, Kyorin Pharmaceutical Co.), cinoxacin (Cinobact, Shionogi Pharmaceutical Co.) and nalidixic acid (Wintomylon, Daiichi Pharmaceutical Co.) (Fig. 1).

Blood samples of 4 ml each were collected from an ear vein in rabbit at 30 min, 1, 2, 3, 4, 5, 6, 7, 9 and 24 hr after an administration of theophylline. The concentrations of theophylline in blood plasma were measured by homogeneous enzyme immunoassay (Emit®, Syva Semi Autonomic System cp 1,000).

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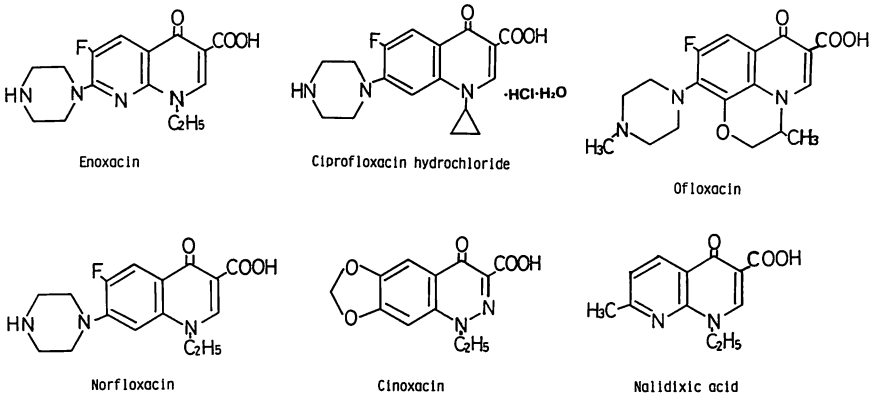

Fig. 1 Chemical structures of new quinolones

Results

Results examined the effects of 6 new quinolones on the blood concentration of theophylline in rabbits are shown in Fig. 2—Fig. 7 and Table 1.

No significant differences in the blood level of theophylline were observed between administrations with and without each new quinolone at both of administration by one shot and administration for 4 consecutive days. Also, no significant changes in AUC of theophylline were observed between the groups with and without coadministrations of new quinolones.

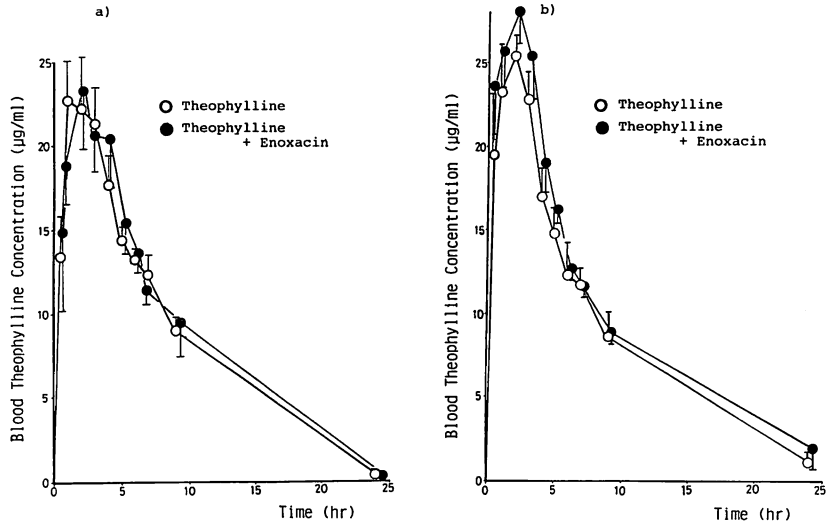

Fig. 2 Effects of enoxacin (20 mg/kg/day) on blood theophylline concentrations in rabbits

Theophylline (20 mg/kg/day) was administered a) one shot and b) for 4 days.
Vertical bars represent standard error of the mean.

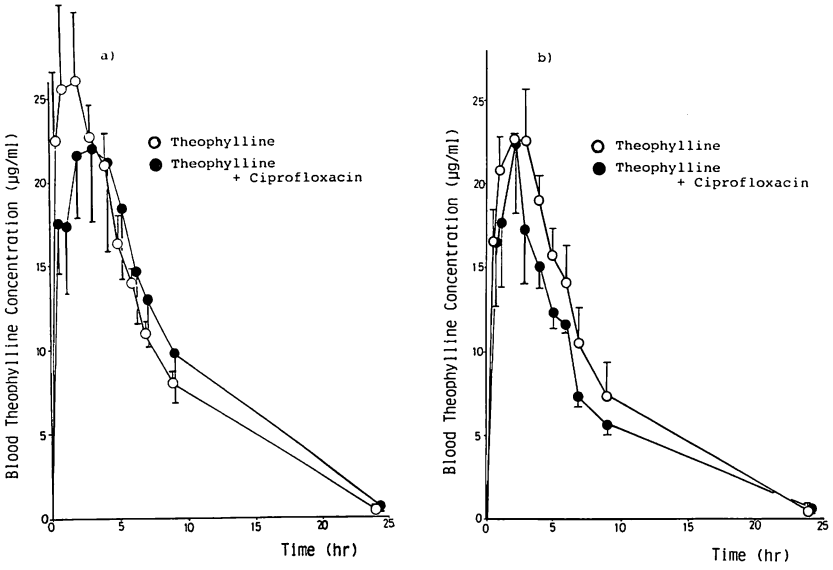

Fig. 3 Effects of ciprofloxacin (20 mg/kg/day) on blood theophylline concentrations in rabbits

Theophylline (20 mg/kg/day) was administered a) one shot and b) for 4 days.
Vertical bars represent standard error of the mean.

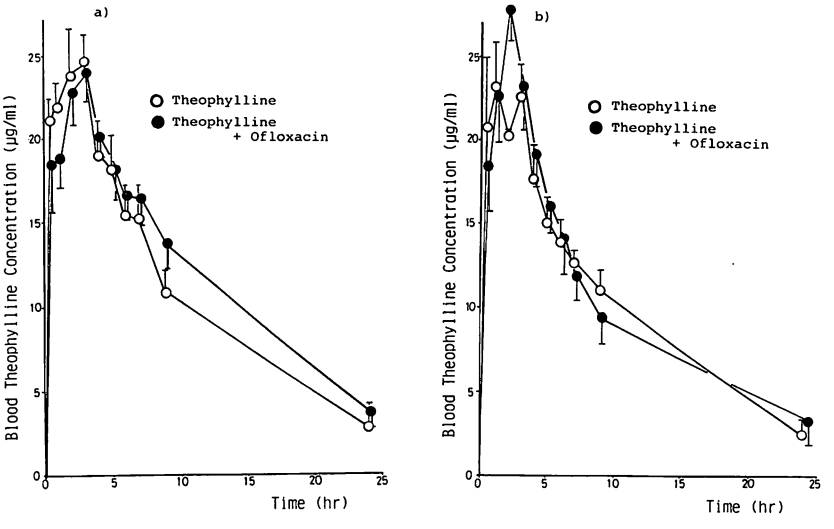

Fig. 4 Effects of ofloxacin (20 mg/kg/day) on blood theophylline concentrations in rabbits

Theophylline (20 mg/kg/day) was administered a) at one shot and b) for 4 days. Vertical bars represent standard error of the mean.

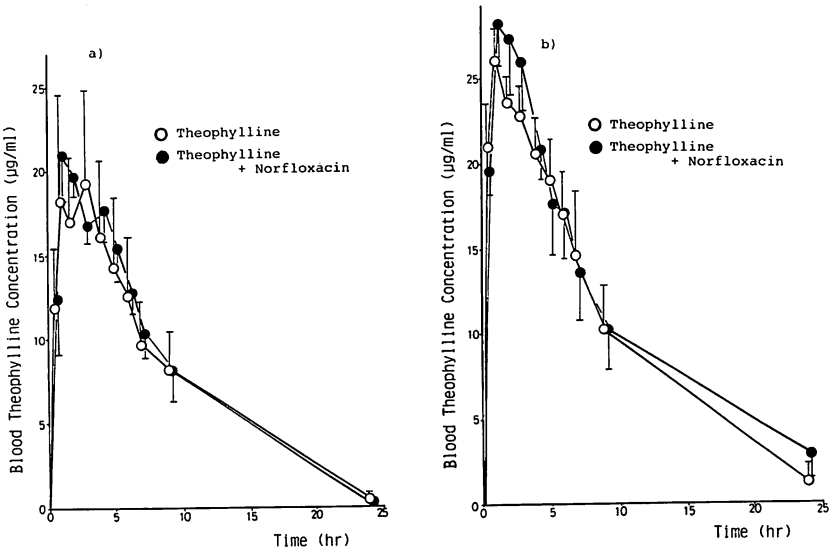

Fig. 5 Effects of norfloxacin (20 mg/kg/day) on blood theophylline concentrations in rabbits

Theophylline (20 mg/kg/day) was administered a) at one shot and b) for 4 days. Vertical bars represent standard error of the mean.

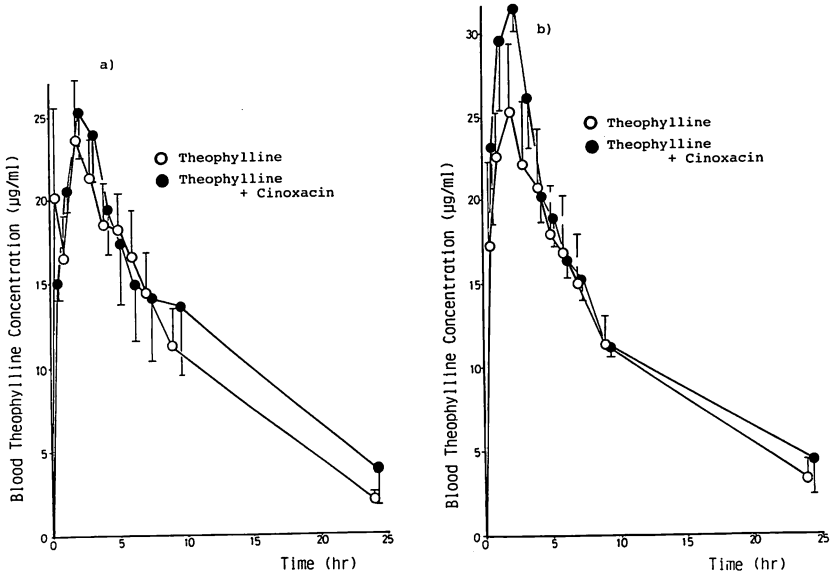

Fig. 6 Effects of cinoxacin (20 mg/kg/day) on blood theophylline concentrations in rabbits

Theophylline (20 mg/kg/day) was administered a) at one shot and b) for 4 days. Vertical bars represent standard error of the mean.

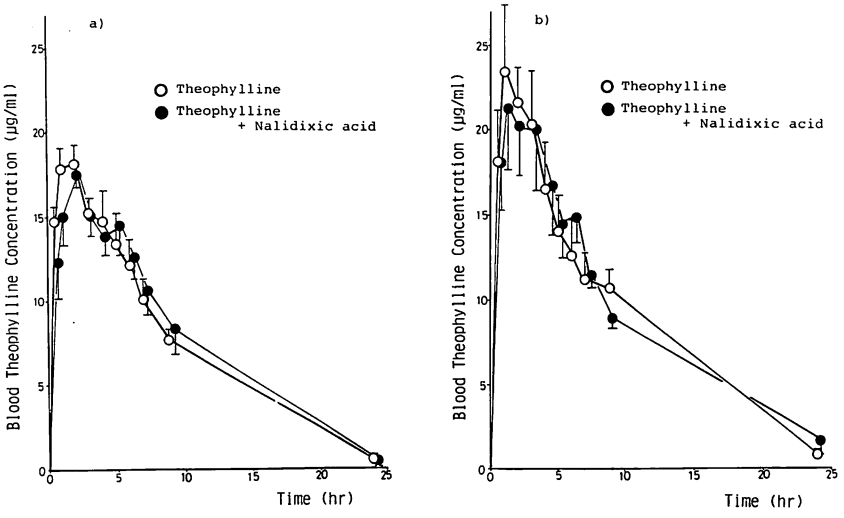

Fig. 7 Effects of nalidixic acid (20 mg/kg/day) on blood theophylline concentrations in rabbits

Theophylline (20 mg/kg/day) was administered a) at one shot and b) for 4 days. Vertical bars represent standard error of the mean.

Discussion

In the case of coadministration of theophylline, enoxacin is known to decrease theophylline clearance by 60 %, to increase the plasma theophylline concentration and cause often adverse reactions[3]. On the other hand, it has been reported that ciprofloxacin, ofloxacin and norfloxacin increased[5-8] or did not change the plasma theophylline concentrations[9-11]. It is known, furthermore, that other new quinolones do not lead to changes of the plasma theophylline levels[10),12),13].

The mechanism by which enoxacin increases the plasma theophylline concentration is entirely unclear, but it might relate to a reduction of hepatic clearance since theophylline is almost completely metabolized in the liver[14]. It has been considered, also, that the interaction of theophylline and enoxacin was largely due to inhibition of theophylline metabolism induced by the 4-oxo metabolite of enoxacin[3),12)]. Although other new quinolones also influence to theophylline clearance, this interaction is significantly smaller than the effect of enoxacin[5-8]. It may be due to magnitude of the inhibition of theophylline metabolism by the 4-oxo metabolite of each new quinolone.

In the present study, the blood theophylline concentration and AUC of theophylline were not affected by coadministration of new quinolones at both of the administration of one shot or for 4 consecutive days in rabbits. Thus, the drug interaction showed clinically was not observed on the experiment in animal. Although this may be due to species difference, it is considered that the production of 4-oxo metabolite of enoxacin in rabbits is lesser than in human.

Table 1 Effects of new quinolones on pharmacokinetic parameters of blood theophylline concentrations in rabbits

(means±S. E.)

	No. of Animals	C_{max}[a)] (μg/ml)	$T_{1/2}$[b)] (hr)	AUC (μg·hr/ml)
Theo (one shot)	6	23.4±2.4	3.6±0.6	211.9±12.1
Theo+Eno	6	25.7±3.1	2.7±0.7	213.7±18.0
Theo (for 4 days)	4	21.5±2.1	4.4±1.3	223.1±19.5
Theo+Eno	4	28.0±1.8	5.5±1.3	241.1±13.5
Theo (one shot)	4	29.5±3.4	3.0±0.5	210.3±15.3
Theo+Cipro	4	21.6±3.2	3.0±0.8	225.9±52.0
Theo (for 4 days)	4	25.8±2.3	3.0±0.9	199.7±13.8
Theo+Cipro	4	22.3±4.0	3.5±1.2	162.8± 6.8
Theo (one shot)	5	26.1±2.1	6.5±1.8	265.1±28.5
Theo+Oflo	5	24.5±1.5	7.6±2.3	288.1±19.7
Theo (for 4 days)	4	24.6±2.7	6.4±1.1	250.5±26.2
Theo+Oflo	4	27.3±1.8	6.7±1.9	244.9±28.3
Theo (one shot)	4	21.5±6.4	4.4±1.9	188.7±47.3
Theo+Norflo	4	22.6±2.0	2.7±0.7	190.2± 3.6
Theo (for 4 days)	4	27.3±1.3	4.0±1.5	252.1±46.0
Theo+Norflo	4	30.6±2.4	6.0±1.6	268.7±44.9
Theo (one shot)	4	25.8±3.4	5.9±0.5	254.3±39.0
Theo+Cino	4	26.7±2.8	7.8±2.1	290.1±66.6
Theo (for 4 days)	4	25.7±3.8	7.5±1.3	311.6±68.2
Theo+Cino	4	33.9±2.4	7.1±1.8	322.1±27.3
Theo (one shot)	4	18.4±1.1	4.1±0.7	179.5±15.4
Theo+Nalid	4	17.8±0.4	3.3±0.7	180.9±17.6
Theo (for 4 days)	4	24.2±3.4	4.2±0.7	226.1±27.2
Theo+Nalid	4	22.9±3.3	6.2±1.7	215.5±15.5

Theo : Theophylline Eno : Enoxacin Cipro : Ciprofloxacin
Oflo : Ofloxacin Norflo : Norfloxacin Cino : Cinoxacin
Nalid : Nalidixic acid

a)Peak blood concentration
b)Biological half-life of elimination phase

The difference of theophylline metabolism in human and rabbits has been observed also by erythromycin[15]. Erythromycin is demethylated by the liver and appears to induce its own metabolism. The metabolite which is formed then binds with cytochrome P-450 forming an inactive complex. It is the P-450 enzyme system which is responsible for the metabolism of

theophylline. The inactivation of P-450 by erythromycin may require several days. The metabolism of theophylline in rabbits is not identical to that in humans. As the reason, it has been considered the species difference might be related to the inactivation of P-450 by erythromycin[15]. Also the difference of theophylline metabolism induced by new quinolones in humans and rabbits may be explained by the similar mechanism to erythromycin.

Furthermore, various physico-chemical properties such as the permeability of cell membrane and the cell affinity of new quinolones may be taken part in this mechanism. At present, we are investigating on the species difference in theophylline metabolism at enzyme level.

Recently, the use of new quinolone antibiotics with the concurrent administration of theophylline has been increased in respiratory tract infections. If concomitant use of both drugs is necessary, the monitoring of plasma theophylline concentration and adverse reactions, and the adjustment of theophylline dose are recommended.

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