Kinetic Interaction between Theophylline and a Newly Developed Quinolone, NY-198

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(Received January 5, 1989)

The effect of a newly developed quinolone, NY-198, on the pharmacokinetics and metabolism of theophylline was investigated under steady-state conditions in six male healthy volunteers, in a crossover fashion. A sustained-release theophylline formulation (200 mg twice daily at 12 h intervals) was received as monotherapy or coadministration with NY-198 (200 mg twice daily at 12 h intervals). No significant change in the pharmacokinetic parameters of theophylline was observed during coadministration of NY-198. No significant change in urinary excretion of theophylline and its metabolites was also observed. These findings indicate that NY-198 does not influence the pharmacokinetics of theophylline and we can suggest that quinolone derivatives have less effect on theophylline disposition than 1, 8-naphthyridine derivatives among quinolones.

Keywords — theophylline; quinolone derivative; NY-198; pharmacokinetic interaction; metabolism

Introduction

Theophylline is widely used as a bronchodilator and respiratory stimulant in the treatment of acute and chronic asthma. For the reasons of its narrow therapeutic range and its severe adverse effects such as nausea, vomiting, and sinus tachycardia, a change in theophylline concentration will have consequence for adequate treatment.

Several investigators have reported that simultaneous treatment with drugs such as allopurinol, cimetidine and erythromycin can caused unwanted effects and recommend a change in the theophylline dose, guided by routine monitoring of theophylline concentration. Recently, an increase in theophylline concentration has been reported with a number of quinolone antibacterial drugs. Especially, the interaction between theophylline and enoxacin has been extensively discussed: enoxacin significantly elevated the theophylline concentration and caused an adverse effect.

The mechanism of reduction of theophylline clearance by quinolone has generally been considered as an inhibition of theophylline metabolism. Moreover, Backmann et al. described renal clearance of theophylline metabolites influenced by the enoxacin comedication. There are therefore a lot of interests in pharmacokinetic interaction between theophylline and quinolones.

Recently, a number of new quinolone antimicrobial agents have been developed. One of these new quinolones, NY-198, illustrated in Fig. 1, has a good in vitro activity against gram-positive and gram-negative bacteria including many organisms resistant to penicillins, cephalosporins, and aminoglycosides. The present study was performed to investigate the influence of NY-198 on the pharmacokinetics of theophylline.

![Fig. 1. Chemical Structure of NY-198](attachment:image.png)
line in healthy male volunteers under steady-state conditions.

Materials and Method

Drugs — Theo-Dur (100 mg of theophylline per tablet; Nikken Kagaku, Tokyo, Japan) as a sustained-release theophylline formation was used in this study. We tested NY-198 in capsule form. Each capsule contained 100 mg of the \((\pm)\)-1-ethyl-6,8-difluoro-1,4-dihydro-7-(3-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid hydrochloride (Shionogi Co., Ltd., Osaka Japan and Central Research Laboratory, Hokuriku Seiyaku Co., Ltd., Fukui, Japan) was used.

Subjects — Characteristics of six healthy men who participated in this study are listed in Table I. They were judged to be healthy on the basis of routine laboratory tests. We obtained informed consent from each person after a full explanation of procedures.

Study Procedure — The study was of the crossover fashion, with each subject receiving as his own control. Throughout the study, they abstained from other xanthine-containing foods and beverages (coffee, tea, chocolate, cola). First, each subject received 200 mg of theophylline twice daily at 12 h intervals (9:00 A.M. and 9:00 P.M.) from day 1 to 9. After steady-state plasma theophylline concentrations were obtained, NY-198 was started in a dose of 200 mg twice a day only for the comedication group: two capsules were ingested at the same time as theophylline for the last 5 days. On the morning of day 10, the last dose of theophylline and NY-198 was administered. Blood samples were taken before, and 1, 2, 4, 6, 8 and 12 h after the last dose. Urine samples were collected during the same period as blood collection. After an interval of 2 weeks without any medication, each subject received another schedule in the crossover fashion.

Assay — Blood samples (5 ml) were collected in glass tubes containing ethylenediaminetetraacetic acid two sodium (EDTA-2Na) and immediately centrifuged to obtain the plasma. The plasma and 10 ml of each urine sample obtained were stored at \(-40^\circ\text{C}\) until analysis. The theophylline concentrations in the plasma were determined by means of high-performance liquid chromatography (HPLC) method previously described.\(^{15}\) Theophylline and three of its metabolites, 3-methylxanthine, 1-methyluric acid, 1, 3-dimethyluric acid in urine were also assayed by a modified HPLC method of Muir et al.\(^{16}\) The concentration of NY-198 in plasma and urine were measured by the HPLC method.\(^{17}\)

Pharmacokinetic Analysis — The area under the plasma concentration-time curve (\(AUC\)) from 0 to 12 h after the last dose was calculated by the trapezoidal rule. The average plasma concentration (\(C_{ss}\)) of theophylline during the dose interval at the last dose was calculated as \(C_{ss} = AUC/12\). Total body clearance and renal clearance were determined \( CL_{sys} = D \times F/AUC, \ CL_{r} = CL_{sys} \times U_{TP} \), respectively, where \(D\) is the theophylline dose adjusted with their body weight (mg/kg), and \(F\) is the bioavailability assumed to be 1.0. \(U_{TP}\) are theophylline unchanged recovery. We also investigated the pharmacokinetic characteristics of NY-198. Unweighted plasma concentration data after multiple oral doses of NY-198 were fitted to a one-compartment open model with first order absorption and elimination by using the following equation:

\[
C = \frac{k_{a}FD}{V_{d}(k_{a}-k_{el})}\left(\frac{1}{1-e^{-k_{el}t}} - \frac{1}{1-e^{-k_{a}t}}\right)
\]

where \(k_{a}\) is the apparent first order absorption rate constant (1/h), \(k_{el}\) is the apparent first

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age (years)</th>
<th>Body weight (kg)</th>
<th>Height (cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T.I.</td>
<td>26</td>
<td>68</td>
<td>173</td>
</tr>
<tr>
<td>N.N.</td>
<td>26</td>
<td>58</td>
<td>172</td>
</tr>
<tr>
<td>T.O.</td>
<td>25</td>
<td>72</td>
<td>175</td>
</tr>
<tr>
<td>T.F.</td>
<td>26</td>
<td>68</td>
<td>178</td>
</tr>
<tr>
<td>I.M.</td>
<td>26</td>
<td>60</td>
<td>170</td>
</tr>
<tr>
<td>T.K.</td>
<td>28</td>
<td>60</td>
<td>162</td>
</tr>
<tr>
<td>Mean</td>
<td>26.2</td>
<td>64.3</td>
<td>171.7</td>
</tr>
<tr>
<td>S.E.M.</td>
<td>0.4</td>
<td>2.3</td>
<td>2.2</td>
</tr>
</tbody>
</table>
order elimination constant (1/h), \( V_d \) is the apparent volume of distribution (1/kg), \( t \) is the time after administration (h) and \( \tau \) is the dosing interval (h).

**Data Analysis** — The values in the present study are expressed as the mean ± S.E.M. and the data are analyzed by means of Student’s paired \( t \)-test with \( p < 0.05 \) taken as the minimum level of significance.

**Results**

Figure 2 shows the mean steady-state plasma theophylline concentration–time data obtained after administration of theophylline alone and after coadministration of NY-198. The mean NY-198 concentration–time data is also shown in the same figure. No significant increase in the theophylline concentrations after coadministration of NY-198 was observed in the six subjects. The pharmacokinetic parameters of theophylline are summarized in Table II. There were no significant differences in the pharmacokinetic parameters of theophylline between those with and without NY-198.

Since theophylline undergoes extensive metabolism, we compared the amounts of theophylline and its major metabolites excreted in the urine after monotherapy with those after coadministration of NY-198 (Table III), in order to investigate the influence of NY-198 on the hepatic metabolism of theophylline. The total urinary recovery of theophylline and its individual metabolites did not change by addition of NY-198.

The pharmacokinetic parameters of NY-198 are listed in Table IV. The rates of absorption and elimination were fitted to an apparent first order process.

Adverse effects during the study were limited

**Table II. Pharmacokinetic Parameters of Theophylline**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>NY-198</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Without</td>
</tr>
<tr>
<td>( C_{ss} (\mu g/ml) )</td>
<td>4.95 ± 0.36</td>
</tr>
<tr>
<td>( C_{ss}^{MAX} (\mu g/ml) )</td>
<td>5.99 ± 0.38</td>
</tr>
<tr>
<td>( T_{max} (h) )</td>
<td>4.67 ± 0.67</td>
</tr>
<tr>
<td>( AUC (\mu g\cdot h/ml) )</td>
<td>59.41 ± 4.26</td>
</tr>
<tr>
<td>( CL_{sys} (ml/kg/h) )</td>
<td>53.75 ± 3.45</td>
</tr>
<tr>
<td>( CL_{r} (ml/kg/h) )</td>
<td>7.14 ± 0.81</td>
</tr>
</tbody>
</table>

Each value represents the mean ± S.E.M. of six subjects. \( C_{ss} = \) average concentration calculated as \( C_{ss} = AUC / 12 \), \( C_{ss}^{MAX} = \) maximum steady-state concentration observed, \( T_{max} = \) time at \( C_{max} \), \( AUC = \) area under the concentration–time curve within the dosage interval, \( CL_{sys} = \) total body clearance calculated as \( CL_{sys} = \text{dose} / AUC \), \( CL_{r} = \) renal clearance calculated as \( CL_{r} = \) theophylline unchanged recovery \( \times \) \( CL_{sys} \).

**Table III. Mean Urinary Recovery of Theophylline and Its Metabolites**

<table>
<thead>
<tr>
<th>Metabolite</th>
<th>NY-198</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Without</td>
</tr>
<tr>
<td>1-MU</td>
<td>25.67 ± 1.71</td>
</tr>
<tr>
<td>3-MX</td>
<td>13.83 ± 2.22</td>
</tr>
<tr>
<td>1, 3-DMU</td>
<td>37.71 ± 1.31</td>
</tr>
<tr>
<td>Theophylline</td>
<td>13.97 ± 2.36</td>
</tr>
<tr>
<td>Total</td>
<td>91.17 ± 3.78</td>
</tr>
</tbody>
</table>

Each value represents the mean ± S.E.M. of six subjects. Values of metabolites are expressed on a molar basis and represent the amount excreted in 12 h as percentage of theophylline dose. 1-MU, 1-methyluric acid; 3-MX, 3-methylxanthine; 1,3-DMU, 1,3-dimethyluric acid.

Fig. 2. Mean Steady-State Plasma Theophylline and NY-198 Concentration–Time Data on Day 10 after Administration of Theophylline Alone and Coadministration of NY-198

O, theophylline alone; ●, theophylline with NY-198; ▲, NY-198. Each value represents the mean ± S.E.M. of six subjects.
to two subjects, who experienced gastrointestinal symptoms caused by NY-198 since no adverse effects were experienced in the monotherapy.

**Discussion**

In the present study, no significant change in pharmacokinetics and metabolism of theophylline after coadministration of NY-198 was observed. This finding suggests that NY-198 can safely be administered to asthmatic patients received chronic therapy with theophylline.

A number of articles concerning the effects of various quinolones on theophylline clearance have been published. It has been reported that the order of the magnitude of the decrease in theophylline clearance induced by quinolones is enoxacin (63%) > ciprofloxacin (30%) > pefloxacin (29%) > norfloxacin (15%) > ofloxacin (12%).\(^8\,\,^{11,\,\,12}\) Regarding the mechanism of the decrease in theophylline clearance induced by quinolones, Wijnands et al.\(^8\) reported a good relationship between the urinary recovery of the 4-oxo metabolite and increased AUC values of theophylline after coadministration of enoxacin, ciprofloxacin, and pefloxacin. They proposed that the 4-oxo metabolite excreted in the urine seems to be mainly responsible for the change in theophylline clearance due to competitive inhibition of the demethylation process of theophylline since the chemical structures of the 4-oxo piperazine are similar to the N1-N3 part of the xanthine molecule. NY-198 tested in the present study was excreted 70.04% in the urine unchanged and the 4-oxo metabolite could not be detected, because the 3 position of piperazine ring is masked by methyl group. As a result of the present study, their hypothesis can be supported.

Thereafter, Edwards et al.\(^18\) reported that the direct administration of 4-oxoenoxacin to rats had no effect on antipyrine clearance, although enoxacin reduced antipyrine clearance by approximately 40%. They proposed that the reduction of theophylline clearance is not due to 4-oxo piperazine but to an intermediate metabolite in the production of 4-oxoenoxacin or some other related metabolite which inhibits theophylline metabolism. However, there is no evidence for the intermediate metabolite or other metabolite correlated with the formation of 4-oxo piperazine. We can propose the hepatic enzyme of the formation from piperazine to 4-oxo to inhibit competitively theophylline metabolism. Moreover, the chemical structure of NY-198 is similar to that of norfloxacin and the only differences are in the presence of a fluorine at position 8 and 3-methyl in the 7-piperazine ring at position 7. It is doubtful that a fluorine at position 8 affects the theophylline disposition because the degree of influence on the theophylline clearance was different with each quinolone derivative despite the fact that all of their derivatives have a fluorine at position 6. It may therefore be suggested that the 3 position of the piperazine ring plays an important role for the interaction with theophylline.

On the other hand, our previous paper\(^14\) showed that a newly developed quinolone, T-3262, which has no formation of the 4-oxo metabolite but significantly decreased theophylline clearance (34%). The chemical structure of T-3262 has 3-amino-1-pyrrolidinyl ring at position 7 of 1, 8-naphthyridine. The percent reduction in theophylline clearance was nearly equal to that of ciprofloxacin and pefloxacin. These results suggest that the interaction between theophylline and quinolones is not only dependent on the 4-oxo metabolite.
Further studies on the relationships between quinolone structures and their interaction with theophylline must be investigated. In a clinical use of antimicrobial agents, these agents were mainly divided into the two groups of 1, 8-naphthyridine and quinoline derivatives. Previous studies demonstrated that the 1, 8-naphthyridine derivative, enoxacin, remarkably decreased theophylline clearance, although the quinoline derivatives, ciprofloxacin, pefloxacin, norfloxacin, ofloxacin, and NY-198 has no effect or a little effect on theophylline clearance. These results indicate that 1, 8-naphthyridines have more influence on theophylline disposition than quinoline derivatives.

Remarkable differences in the pharmacokinetic parameters between NY-198 and norfloxacin are observed, although these chemical structures are similar: The half-life of norfloxacin was shown to be 3.5 h (NY-198; 5.26 h) and approximately 30% of the norfloxacin oral dose was excreted unchanged in the urine and other metabolites were excreted only less than 20% of the parent drug\(^1\) (NY-198; 70.04%). The peak serum levels of 0.75 μg/ml are achieved after the same dose of this study\(^2\) (NY-198; 1.663 μg/ml). These results indicate that NY-198 has a long half-life and a good absorption compared to norfloxacin. The present study concluded that NY-198 would be useful for the treatment of patients with various infections and also with asthmatic patients during chronic theophylline therapy.

References