Studies on the Mechanism of Pharmacokinetic Interaction of Aluminum hydroxide, an Antacid, with New Quinolones in Rats

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Summary

The studies on the mechanism of pharmacokinetic interaction of aluminum hydroxide with new quinolones, ofloxacin, enoxacin and norfloxacin, were performed in rats. New quinolones (20 mg/kg) were administered orally with or without aluminum hydroxide or aluminum chloride (50 mg/kg). Co-administration of aluminum hydroxide induced a significant decrease in Cmax of enoxacin and norfloxacin, and in the AUC values of the three drugs. This effect was enhanced by co-administration of aluminum chloride. The combination of aluminum hydroxide caused a significant increase in the intestinal contents and decrease in urinary excretion of new quinolones. The formation of the stable chelate of new quinolones with Al3+ ions formed from aluminum hydroxide in the same acidic solution as gastric juice was observed. Thus, it is concluded that the co-administration of aluminum hydroxide affects the pharmacokinetics of new quinolones, probably, by the inhibition of the intestinal absorption of new quinolones by the chelate formation of these compounds with Al3+ ions released from aluminum hydroxide in the gastric juice.
Introduction

The introduction of new quinolones to the chemotherapy of patients with various infectious diseases has brought out not only their outstanding chemotherapeutic effectiveness against the diseases, but also undesirable adverse reactions of the drugs. A major adverse reactions of new quinolones have shown to be gastrointestinal symptoms including nausea and vomiting (1). In order to suppress these symptoms, aluminum- or magnesium-containing antacids have been used frequently by the concomitant administration. However, it has been demonstrated recently that the co-administration of the antacids, including aluminum hydroxide, affects adversely the oral absorbability of various new quinolones in human subjects (2-8). Although many investigators have suggested the chelate formation of new quinolones with metal ions in the gastrointestinal tract as the mechanism of the inhibition of absorption of the drugs, details of the pharmacokinetic interaction of the antacids with new quinolones remain unknown so far. Therefore, mechanistic studies on pharmacokinetic interaction of aluminum hydroxide with new quinolones were carried out.

This paper describes the results on the effect of concurrent administration of aluminum hydroxide or aluminum chloride on the pharmacokinetics of ofloxacin, enoxacin and norfloxacin in rats, and on the formation of chelates of new quinolones with various metal ions.

Experimental

Drugs and Reagents

Ofloxacin (Daiichi Seiyaku Co., Ltd., Tokyo, Japan), enoxacin (Dainippon Pharmaceutical Co., Ltd., Osaka, Japan), norfloxacin (Kyorin Pharmaceutical Co., Ltd., Tokyo, Japan), and aluminum hydroxide (Chugai Pharmaceutical Co., Ltd., Tokyo, Japan) were used in this study. 14C-labelled ofloxacin ((±)-9-fluoro-2, 3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-7 H-pyrido [1, 2, 3-de] [1, 4] [6-14C] benzoxazine-6-carboxylic acid, 14C-ofloxacin) was also used for the experiments. Other materials and solvents were of analytical grade.

Animals

Male Sprague-Dawley strain rats weighing 170-200 g (Shizuoka Agricultural Coop. Ass., Hamamatsu, Japan) were used for the experiments. The animals received a rat diet (Funabashi Farms, F-2, Japan) and water ad libitum and were kept at controlled conditions (23±2°C and 55±10% humidity). All animals fasted for 16 hours prior to dosing and for 4 hours post dosing.

Administration of Drugs

Ofloxacin, enoxacin, norfloxacin and aluminum hydroxide were prepared as a suspension in 0.5% sodium carboxymethyl cellulose solution, and aluminum chloride was dissolved in distilled water. Three rats in a group received a single oral dose of 20 mg/kg of ofloxacin or 14C-ofloxacin, enoxacin and norfloxacin with or without 50 mg/kg of aluminum hydroxide or aluminum chloride. For measurement of ofloxacin in gastrointestinal contents, 14C-labelled ofloxacin was given to another group of animals.
Sampling

After dosing, blood samples were taken from the jugular vein under light anesthesia with ether at various time intervals. For the collection of urine, another group of animals received the drug, and were individually placed in the metabolism cage. Stomach and intestine were removed from rats after sacrifice by exanguination at the carotid, and gastric and intestinal contents were obtained after washing the tissue with saline.

Measurements

Concentrations of ofloxacin in the serum and urine were determined by HPLC method (9). Quantitation of enoxacin and norfloxacin was carried out by the methods of Vree et al. (10) and Forchetti et al. (11), respectively. Analyses of radioactivity in serum and gastrointestinal contents were performed with a liquid scintillation spectrometer (Model LSC-900, Aloka Co., Ltd.). The quentioning was corrected with an automatic external standard method. Concentrations of Al\textsuperscript{3+} ions in the solution were measured as follows: aluminum hydroxide, suspended in acidic solution, was incubated and stirred for 10 minutes at 37°C and were filtrated with filter (Nihon Millipore Kogyo K.K., pore size 0.22 \(\mu m\)). Al\textsuperscript{3+} concentrations in the filtrates were determined by atomic absorption spectrometry (Hitachi, Z-8000 Polarized Zeeman Atomic Absorption Spectrophotometer). The stability constants of new quinolone-metal chelates were measured by the titration method (12). The composition of sample solution was made of 50 ml of 2.5 \(\times 10^{-4}\) M new quinolones, 0.5 ml of 1.25 \(\times 10^{-2}\) M metal ions and 1.5 ml of 2.5 \(\times 10^{-5}\) M HClO\textsubscript{4}. The titration was conducted by addition of 1.25 \(\times 10^{-2}\) N KOH with a automatic titrator (Mitsubishi Kasei Kogyo K.K., GT-05) at 25°C. Nitrogen gas was passed through during titration in order to exclude CO\textsubscript{2} from the solution.

Calculations

Statistical analysis was carried out by the Student’s t-test. Calculation of stability constants were performed by the use of the private program and computor in accordance with complexity of calculation.

Results

Effect of Combination of Aluminum hydroxide or Aluminum chloride on Serum Concentrations of New Quinolones

As shown in Fig. 1, serum concentrations of ofloxacin, enoxacin and norfloxacin were decreased significantly up to 2 hours after dosing together with aluminum hydroxide. This combination effect on the serum concentrations of ofloxacin was more pronounced by the concurrent administration of aluminum chloride instead of aluminum hydroxide.

Table I shows the results on the effect of combination of aluminum hydroxide or aluminum chloride on the pharmacokinetic parameters of ofloxacin, enoxacin and norfloxacin. Concurrent administration of aluminum hydroxide induced a significant decrease in \(C_{\text{max}}\) of enoxacin and norfloxacin, and a significant decrease in AUC values of these three drugs. Co-administration of aluminum chloride caused a significant decrease in \(C_{\text{max}}\), a significant prolongation of \(T_{\text{max}}\), and a significant increase in AUC of ofloxacin. This combination effect of aluminum chloride on the pharmacokinetic parameters of ofloxacin was much larger than that of aluminum hydroxide.
Fig. 1. Effect of aluminum hydroxide (AL) or aluminum chloride (AlCl₃) on serum concentrations of ofloxacin (OFLX), enoxacin (ENX) and norfloxacin (NFLX) in rats.

○: new quinolones (20 mg/kg) alone, ■: new quinolones (20 mg/kg) with aluminum hydroxide (50 mg/kg) or AlCl₃ (50 mg/kg).

* P<0.05, ** P<0.01, § P<0.001 : significantly different from new quinolones alone.

Table I. Effect of aluminum hydroxide (AL) or aluminum chloride (AlCl₃) on pharmacokinetic parameters of ofloxacin (OFLX), enoxacin (ENX) and norfloxacin (NFLX).

<table>
<thead>
<tr>
<th>Group</th>
<th>C&lt;sub&gt;max&lt;/sub&gt; (µg/ml)</th>
<th>T&lt;sub&gt;max&lt;/sub&gt; (h)</th>
<th>AUC&lt;sub&gt;0-t&lt;/sub&gt; (µg·h/ml)</th>
</tr>
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<tbody>
<tr>
<td>OFLX&lt;sup&gt;1)&lt;/sup&gt;</td>
<td>10.8 ±0.62</td>
<td>0.19±0.06</td>
<td>22.0 ±0.72&lt;sup&gt;2)&lt;/sup&gt;</td>
</tr>
<tr>
<td>OFLX&lt;sup&gt;1)&lt;/sup&gt;+AL</td>
<td>8.58±0.63</td>
<td>0.25±0.00</td>
<td>17.6 ±0.08&lt;sup&gt;**&lt;/sup&gt;</td>
</tr>
<tr>
<td>ENX</td>
<td>3.60±0.11</td>
<td>0.50±0.00</td>
<td>6.02±0.16&lt;sup&gt;3)&lt;/sup&gt;</td>
</tr>
<tr>
<td>ENX+AL</td>
<td>2.49±0.11&lt;sup&gt;**&lt;/sup&gt;</td>
<td>0.36±0.14</td>
<td>4.33±0.20&lt;sup&gt;**&lt;/sup&gt;</td>
</tr>
<tr>
<td>NFLX</td>
<td>0.88±0.08</td>
<td>0.50±0.00</td>
<td>0.99±0.07&lt;sup&gt;3)&lt;/sup&gt;</td>
</tr>
<tr>
<td>NFLX+AL</td>
<td>0.59±0.02&lt;sup&gt;*&lt;/sup&gt;</td>
<td>0.33±0.08</td>
<td>0.42±0.04&lt;sup&gt;**&lt;/sup&gt;</td>
</tr>
<tr>
<td>OFLX&lt;sup&gt;2)&lt;/sup&gt;</td>
<td>3.32±0.07</td>
<td>0.25±0.00</td>
<td>4.58±0.12&lt;sup&gt;4)&lt;/sup&gt;</td>
</tr>
<tr>
<td>OFLX&lt;sup&gt;2)&lt;/sup&gt;+AlCl₃</td>
<td>0.36±0.02&lt;sup&gt;**&lt;/sup&gt;</td>
<td>1.00±0.00&lt;sup&gt;**&lt;/sup&gt;</td>
<td>1.43±0.11&lt;sup&gt;**&lt;/sup&gt;</td>
</tr>
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</table>

Each value represents the mean±standard error for 3 rats. The fasted animals received an oral dose of new quinolones (20 mg/kg) with or without AL (50 mg/kg) or AlCl₃ (50 mg/kg). 1) The animals received 14C-labeled OFLX. 2) The animals received non-labeled OFLX. a) AUC<sub>0-24h</sub>. b) AUC<sub>0-4h</sub>. c) AUC<sub>0-8h</sub>. d) AUC<sub>0-2h</sub>. * P<0.05 and ** P<0.01 vs. new quinolones alone.

Effect of Combination of Aluminum hydroxide or Aluminum chloride on the Gastrointestinal Contents of Ofloxacin

As shown in Fig. 2, the intestinal contents of ofloxacin were increased significantly up
to 3 hours after the concurrent administration of aluminum hydroxide, while the gastric contents of the drug did not change significantly by the same treatment.

**Effect of Combination of Aluminum hydroxide on the Urinary Excretion of New Quinolones**

As presented in Table II, the co-administration with aluminum hydroxide produced a significant decrease in the urinary excretion of ofloxacin and enoxacin over a period of 8-24 hours after administration. Urinary excretion of norfloxacin was reduced significantly by the concurrent administration of aluminum hydroxide throughout the experimental period.

**Formation of Stable Chelates of New Quinolones with Aluminum Ions**

As shown in Fig. 3, aluminum ions were formed, in approximately 10%, from aluminum hydroxide suspended at the concentration of 10 mg/ml in almost the same acidic solution (pH 1.0) as the rat gastric juice.
Fig. 3. Formation of aluminum ions from aluminum hydroxide (AL) under various concentrations of aluminum hydroxide, and various pH (−log [H⁺]) at 37°C for 10 min.

Table III. Stability constants of new quinolone metal chelates.

<table>
<thead>
<tr>
<th>Metal ion</th>
<th>Ofloxacin</th>
<th>Norfloxacin</th>
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<tbody>
<tr>
<td>Al³⁺</td>
<td>11.1</td>
<td>11.5</td>
</tr>
<tr>
<td>Cu²⁺</td>
<td>10.9</td>
<td>11.4</td>
</tr>
<tr>
<td>Zn²⁺</td>
<td>5.3</td>
<td>5.8</td>
</tr>
<tr>
<td>Mg²⁺</td>
<td>4.3</td>
<td>4.9</td>
</tr>
</tbody>
</table>

Table III indicates the results on stability constants of chelates of new quinolones with various kinds of metal ions. The stability constants of ofloxacin and norfloxacin complexes with Al³⁺ ions were 11.1 and 11.5, respectively, and were similar to those formed with Cu²⁺ ions. Thus, the formation of stable chelates of ofloxacin and norfloxacin with Al³⁺ ions was observed. The measurement of the stability constants of chelates of enoxacin with metal ions could not be carried out because of low solubility of the drug in water. On the other hand, stability constants of ofloxacin and norfloxacin with Mg²⁺ ions were very small, thus indicating that the both drugs did not practically form their chelates with Mg²⁺ ions.

Discussion

In the present study, it has been demonstrated that the co-administration with aluminum hydroxide induces a significant decrease in the rat serum concentrations of new quinolones which results in a significant decrease in their Cmax and AUC, and a significant decrease in the urinary excretion of new quinolones due to the inhibition of intestinal absorption of the drugs. In addition, this combination effect has been shown to be enhanced by the concurrent administration with aluminum chloride instead of aluminum hydroxide, thus suggesting that Al³⁺ ions play a major role in the inhibition of intestinal absorption of new quinolones.
In many cases, Mg(OH)₂—Al(OH)₃ gel (Maalox) has been used so far for the therapy of gastrointestinal symptoms, and has affected the intestinal absorption of new quinolones (3-7). However, it remains unknown which metal ions can affect the intestinal absorption of the drugs. In this regard, the present results have clarified that Al³⁺ ions form the stable chelates with new quinolones, but not with Mg²⁺ ions. Accordingly, it is clear from the present results that the formation of chelates of new quinolones with Al³⁺ ions causes a significant decrease in the intestinal absorption of the drugs.

It has been reported that Al³⁺ ions reduce Cₘₐₓ and prolong the time to reach Cₘₐₓ (Tₘₐₓ) without affecting AUC by delaying the gastric emptying of the concomitant drugs (13-15). However, the interaction of new quinolones with aluminum hydroxide is not the case, because the present results have shown that the combination of aluminum hydroxide does not affect the gastric emptying of ofloxacin. It is considered that the insufficient amount of aluminum ion to delay the gastric emptying rate is produced in the stomach after an oral administration of aluminum hydroxide.

Thus, it is concluded that the pharmacokinetic interaction of aluminum hydroxide with new quinolones may be caused by the inhibition of the intestinal absorption of these drugs due to the stable chelate formation of the drugs with Al³⁺ ions released from aluminum hydroxide in the gastric juice.

References


