THE BIOAVAILABILITIES OF ASPIRIN FROM AN ASPIRIN ALUMINUM AND AN ASPIRIN TABLETS AND THE EFFECTS OF FOOD AND ALUMINUM HYDROXIDE GEL

NAHOKO KANIWA, HIROYASU OGATA, NOBUO Aoyagi and AKIRA Ejima

Division of Drugs, National Institute of Hygienic Sciences, 18-1, Kamiyoga 1-chome, Setagaya-ku, Tokyo 158, Japan

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The bioavailability of aspirin from an aspirin aluminum tablet was compared with that from an aspirin tablet in humans by determining total salicylate excreted in the urine. The effects of concomitant intakes of antacid or food on the bioavailability of aspirin were also investigated. The bioavailability of aspirin from an aspirin aluminum tablet was nearly 60% of that from an aspirin tablet. The low bioavailability of aspirin from an aspirin aluminum tablet was caused by slow release of aspirin from the aluminum complex, and not increased by concomitant intake of food. Intake of food, however, reduced both rate and extent of bioavailability of aspirin from an aspirin tablet, but dried aluminum hydroxide gel granules had no effect on the bioavailability of it.

Keywords—bioavailability in humans; aspirin tablet; aspirin aluminum tablet; effects of food and antacid; dissolution rate

INTRODUCTION

Gastro-intestinal side effects of anti-inflammatory agents are well documented.1,2) Aspirin (I) is known to show the severe gastric side effect, and aspirin aluminum (II) has been used instead of I. II is said to have advantages over I such as greater stability, and absence of acetic odor and gastric side effect, because of its relative inertness.3) II in a powder form, however, was found to have not only a lower absorption rate but also a lower extent of absorption compared with those of I powder.4) It seemed probable that bioavailability of I from a II tablet was lower than that from II powder, and therefore, we determined the bioavailability and dissolution rate of I from a II tablet compared with those from a I tablet. The effect of intake of food or antacid on the bioavailability of I was also investigated, since patients were often recommended to take it with antacid or after a meal to prevent gastric side effects of the drug.

MATERIALS AND METHODS

Materials—I and II tablets (JPIX) were purchased on the open market of Japan. The contents of I in both tablets were 491.3 and 343.3 mg, respectively. I (JPIX), II (JPIX) and dried aluminum hydroxide gel (III) granules (JPIX) were used. All other chemicals were of reagent grade.

Bioavailability Study—Six healthy male volunteers, aged between 23 and 51, weighing between 54 and 69 kg, participated in the study. A randomized block design was employed for the following five treatments;

Treatment A: a I tablet in the fasting state
Treatment B: a I tablet and III granules (0.3 g) in the fasting state
Treatment C: a I tablet in the nonfasting state
Treatment D: a II tablet in the fasting state
Treatment E: a II tablet in the nonfasting state

After overnight fasting, subjects received orally a I or a II tablet with 200 ml of water in the fasting state, or 30 minutes after standard breakfast in the nonfasting state. The standard breakfast consisted of 100 g of bread, 20 g of butter, a boiled egg, 35 g of cucumber and 200 ml of milk. Subjects did not eat for 4 hours after receiving drugs, and then took
food and drink ad libitum. Urine samples were collected at appropriate intervals and stored frozen until assay.

**Analytical Method** — All the metabolites excreted in the urine were hydrolyzed to free salicylate and then were determined as follows\(^4\): Three ml of a urine sample and 2 ml of conc. hydrochloric acid were sealed in an ampule. The ampule was kept in an oil-bath at 100°C for 17 hours, and then the solution was transferred to a test tube with 2 ml of water. 0.5 ml 6N HCl was added to the test tube, and free salicylate was extracted into 4 ml of chloroform. Three ml of organic phase was re-extracted with 6 ml of Trinder’s reagent (4% Fe(NO\(_3\))\(_3\)·9H\(_2\)O in 1 N HCl). The absorbance of salicylate-ferric ion complex in aqueous phase was measured at 540 nm. Calibration curves were drawn using standard I solution, and the amount of I eliminated in the urine was calculated.

**Dissolution Rate** — The dissolution rates of I from a I and a II tablets were determined by oscillating basket,\(^5\) rotating basket and paddle (USPXIX) methods using 900 ml of disintegration test medium No. 1 (JPXIX) at pH 1.2. I and salicylic acid dissolved were determined as follows: The test solution was sampled at appropriate intervals, and 0.5 ml of sample solution filtered through a millipore filter (pore size=1.0 μm) was diluted with 5 ml of 0.1 N NaOH. After standing at room temperature for 30 minutes, the absorbance at 290 nm was measured.

**RESULTS AND DISCUSSION**

Fig. 1 shows average cumulative amount of urinary excretion-time curves after each treatment. The bioavailability parameters and results of ANOVA and multiple range test by l.s.d. (least significant difference)\(^6\) are summarized in Table I. The excretion rate of I at the midpoint between the sampling times (\(V_t\)) and cumulative amount of urinary excretion in 24 hours (\(E_{24}\)) and its infinity (\(E_\infty\))\(^7\) were calculated as follows:

\[
V_t \text{ (%/h)} = \frac{U_{24} \times 100}{A \times (T_n - T_{n-1})}
\]

\[
E_{24} \text{ (%) } = \frac{U_{24} \times 100}{A}
\]

\[
E_\infty \text{ (%) } = E_{24} + \frac{\dot{V}_{24}}{k_{el} \times A}
\]

\(U_{24}\) : mg of I excreted in the urine during the sampling time (\(T_n - T_{n-1}\))

\(A\) : mg of I content in a tablet

\(T_n\) : the \(n\)th sampling time

\(T_{n-1}\) : the \((n-1)\)th sampling time

\(\dot{V}_{24}\) : calculated V at 24 h

\(k_{el}\) : elimination rate constant

The cumulative amount of urinary excretion curves after treatments A (a I tablet administered in the fasting state) and B (a I tablet co-administered with III in the fasting state) was almost the same, and no significant difference was recognized in the bioavailability parameters between both treatments. Both treatments showed higher values of initial excretion rates (\(V_{0.25}, \dot{V}_{1.0}, \dot{V}_{2.0}\) and \(\dot{V}_{3.0}\)), the maximum excretion

![Graph](image-url)  
**FIG. 1. Average Cumulative Amount of Urinary Excretion — Time Curves of Total Salicylate after Each Treatment**

○ a I tablet in the fasting state; ○ a I tablet with 0.3 g of III in the fasting state; ● a I tablet in the nonfasting state; △ a II tablet in the fasting state; ▲ a II tablet in the nonfasting state.
rates \( V_{\text{max}} \), \( E_{24} \) and \( E_{\infty} \). The values of \( V_{0.25}, V_{1.0} \) and \( E_{\infty} \) after treatment C (a 1 tablet administered in the nonfasting state) were significantly lower than those after treatments A and B. But no significant difference was recognized in \( V_{\text{max}} \) among these three treatments. On the other hand, treatments D and E, in which a II tablet was administered in the fasting and nonfasting state, respectively, showed extremely low values of initial excretion rates, \( V_{\text{max}}, E_{24} \) and \( E_{\infty} \) than other treatments where a I tablet was administered. No significant difference was detected between treatments D and E.

All metabolites of I in the urine were hydrolyzed to salicylate to react with Trinder’s reagent by the method used in this study, though they tended to be over-estimated slightly because of urine blank. I after treatments A and B seemed to be absorbed completely, since the recoveries of total salicylate in the urine at infinity were approximately 100%. On the other hand, only 60% of I was absorbed from a II tablet, and this value was less than the value (80%) from II powder previously reported. The absorption rate of I from a II tablet was also significantly slower than from a I tablet. The results of dissolution tests (Table II) showed that the slower and lower bioavailability of I from a II tablet might be due to the slow release of I from II in the gastro-intestinal tract, and it was not improved with concomitant intake of food. These results were the same as those obtained in the study on aluminum flufenamate. As II and aluminum flufenamate are insoluble in water, the rate determining step of the absorption of I and flufenamic acid may be in the stage of release of free acids from their aluminum complexes. Food enhances the bioavailabilities of drugs such as griseofulvin, nitrofurantoin, or chloramphenicol, especially with the dosage form having poor dissolution characteristics, perhaps because of enhanced dissolution rates. The release of I and flufenamic acid from the aluminum complexes was not enhanced by food. The relative bioavailability of aluminum complex to that of free acid, however, was higher in II compared with that in aluminum flufenamate, because the I dissolution rate from a II tablet was faster than that of flufenamic acid from an aluminum flufenamate tablet. II was considered to release the free acid more easily than aluminum flufenamate.

The same result as previous studies was

<table>
<thead>
<tr>
<th>Parameter</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
<th>Result of ANOVA</th>
<th>Multiple range test by l.s.d.</th>
</tr>
</thead>
<tbody>
<tr>
<td>( V_{0.25} ) (%/h)</td>
<td>3.62</td>
<td>3.11</td>
<td>0.82</td>
<td>0.41</td>
<td>0.09</td>
<td>( p &lt; 0.01 )</td>
<td>A &gt; B &gt; C &gt; D &gt; E</td>
</tr>
<tr>
<td>( V_{1.0} )</td>
<td>9.47</td>
<td>10.14</td>
<td>4.45</td>
<td>2.81</td>
<td>2.12</td>
<td>( p &lt; 0.01 )</td>
<td>B &gt; A &gt; C &gt; D &gt; E</td>
</tr>
<tr>
<td>( V_{2.0} )</td>
<td>10.14</td>
<td>10.15</td>
<td>7.73</td>
<td>3.81</td>
<td>3.65</td>
<td>( p &lt; 0.01 )</td>
<td>B &gt; A &gt; C &gt; D &gt; E</td>
</tr>
<tr>
<td>( V_{3.0} )</td>
<td>9.53</td>
<td>10.39</td>
<td>8.94</td>
<td>4.77</td>
<td>5.50</td>
<td>( p &lt; 0.01 )</td>
<td>B &gt; A &gt; C &gt; D &gt; E</td>
</tr>
<tr>
<td>( V_{4.0} )</td>
<td>8.58</td>
<td>9.88</td>
<td>9.48</td>
<td>5.21</td>
<td>4.57</td>
<td>( p &lt; 0.01 )</td>
<td>B &gt; C &gt; A &gt; D &gt; E</td>
</tr>
<tr>
<td>( V_{5.0} )</td>
<td>9.48</td>
<td>10.83</td>
<td>8.16</td>
<td>4.68</td>
<td>5.24</td>
<td>N.S.</td>
<td></td>
</tr>
<tr>
<td>( V_{\text{max}} ) (%/h)</td>
<td>11.05</td>
<td>12.50</td>
<td>10.60</td>
<td>7.59</td>
<td>6.09</td>
<td>( p &lt; 0.05 )</td>
<td>B &gt; A &gt; C &gt; D &gt; E</td>
</tr>
<tr>
<td>( T_{\text{max}} ) (h)</td>
<td>2.33</td>
<td>3.0</td>
<td>2.83</td>
<td>6.33</td>
<td>4.38</td>
<td>( p &lt; 0.01 )</td>
<td>A &lt; C &lt; B &lt; E &lt; D</td>
</tr>
<tr>
<td>( E_{24} ) (%)</td>
<td>102.22</td>
<td>105.00</td>
<td>87.71</td>
<td>65.22</td>
<td>50.38</td>
<td>( p &lt; 0.01 )</td>
<td>B &gt; A &gt; C &gt; D &gt; E</td>
</tr>
<tr>
<td>( E_{\infty} ) (%)</td>
<td>111.22</td>
<td>108.55</td>
<td>93.81</td>
<td>65.94</td>
<td>51.73</td>
<td>( p &lt; 0.01 )</td>
<td>A &gt; B &gt; C &gt; D &gt; E</td>
</tr>
</tbody>
</table>

a) Excretion rate at \( t \) h. b) The maximum excretion rate. c) The time of the maximum excretion rate. d) Cumulative amount of urinary excretion in 24 h. e) Cumulative amount of urinary excretion at infinity. f) The mean values for treatments not underscored by the same line differ significantly.
obtained, i.e., the absorption rate of I from a I tablet was lowered by concomitant intake of food, perhaps as result of reducing gastric emptying rate. A significantly low extent of bioavailability from I tablet in the nonfasting state was also detected in this study compared with that in the fasting state. The relative extent of bioavailability after intake of food was about 85% of that in the fasting state. Impairment of the extent of bioavailability of I may be expected to result from adsorption of the drug to food. Concomitant intake of food also reduced slightly the rate and extent of bioavailability of I from a II tablet, but the effect was not significant statistically.

Contrary effects of antacids on the bioavailability of I have been reported. I was shown to be absorbed more quickly from antacid-buffered preparations. On the other hand, the serum concentrations of salicylate were lowered because of increased renal clearance owing to the elevated urinary pH by antacids. In this study, however, no effects of III granules on the bioavailability of I from a I tablet was observed.

In summary, a II tablet had a very low bioavailability nevertheless the severe gastric side effects of I is largely reduced, and the bioavailability was not increased by concomitant intake of food. I bioavailability from a I tablet was reduced slightly (15%) by food intake, though it was still higher than that from a II tablet. On the other hand, intake of III granules did not affect the bioavailability of I from a I tablet. So co-administration of a I tablet with III granules or administration of a I tablet in the nonfasting state may produce good bioavailability with reduced gastric distress and irritation. We may get also the same plasma level of salicylate with reduced side effects, when the dose of a II tablet administered is increased twofold.

REFERENCES


