THE BIOAVAILABILITY OF FLUFENAMIC ACID FROM ALUMINUM FLUFENAMATE TABLET AND FLUFENAMIC ACID CAPSULE, AND THE INFLUENCE 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 bioavailabilities of flufenamic acid (I) from a commercial aluminum flufenamate (II) tablet and I capsule were estimated by measuring urinary excretion of I and its metabolites fluorometrically. The dissolution rates of I from both dosage forms were also determined. The effects of concomitant intake of food or antacid on the bioavailabilities from the II tablet and the I capsule were investigated. The extent on I bioavailability from the II tablet was less than 30% of that from the I capsule. Dissolution tests suggested that the low bioavailability of I from II tablet resulted from the extremely slow release of I from the II complex. Intake of a standard meal retarded I absorption from I capsule, but did not affect that from the II tablet. Ingestion of dried aluminum hydroxide gel granules had little effect on I bioavailability from the I capsule.

**Keywords** — bioavailability in humans; aluminum flufenamate tablet; flufenamic acid capsule; effects of food and antacid; dissolution rate

INTRODUCTION

Flufenamic acid (I) is often used in therapy of rheumatoid arthritis, but sometimes multiple dose therapy is associated with gastric distress and irritation. Alummiun flufenamate (II) had been developed to avoid the side effects of I and it is used very frequently in Japan. Since II is practically insoluble in water and gastric juice, it seldom causes gastric disturbances, I is slowly released from II and absorbed in the intestine.

Previously we determined the dissolution rates of I from some commercially available I preparations and found that the dissolution rate of I from a II tablet was much slower than that from I capsules. Since Levy and Sahli reported that the bioavailability of aspirin from aspirin aluminum was much lower than that from aspirin due to its low dissolution rate, it seemed possible that the bioavailability of I from the II tablet was lower than from I capsules. In this work, we compared the dissolution rates and bioavailability of I from the II tablet and the I capsule.

In I therapy, it is often recommended that patients should receive the drug immediately after food or antacid intake to prevent gastric side effects. Thus we also investigated the effects of concomitant intakes of antacid or food on I bioavailability.

MATERIALS AND METHODS

**Materials** — The I (100 mg) capsule, the II (125 mg) tablet and dried aluminum hydroxide (III) gel granules are commercially available in Japan. The I capsule used was previously shown to have the highest I bioavailability among the preparations tested. I (Kongo Kagaku Co., Ltd., Toyama) and II (Taisho Pharmaceutical Co., Ltd., Tokyo) were used as received. All other chemicals were of reagent grade.

**Content of Capsules and Tablets** — I Capsule: The contents of five capsules were weighed and a 50 mg sample was dissolved in 50 ml of methanol. After filtration and dilution with methanol, the absorption at 290 nm, \( \lambda_{\text{max}} \), of the sample and
standard solutions were measured.\(^6\)

II Tablet: The aluminum complex was decomposed to I by the method of Inoue et al.\(^8\) Five tablets were weighed and a 60 mg sample was dissolved in 50 ml of 0.5% NaF-methanol solution containing hydrochloric acid. The mixture was shaken for 20 min, filtered, and diluted with methanol, and then free I was determined.

The mean contents per capsule and tablet were 100.1 mg and 116.3 mg as free acid, respectively.

**Bioavailability Study** — Six male volunteers, aged 23 to 51, weighing 54 to 69 kg, participated in the study, and an informed consent was obtained from each subject. None of them had a history of renal or hepatic disease and clinical examinations gave normal results. A randomized block-design was employed for the following five treatments:

- **treatment B:** A I capsule and III gel (0.3 g) in the fasting state
- **treatment C:** A I capsule 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 a I capsule or a II tablet orally with 200 ml of water in the fasting state or 30 min after breakfast. The standard breakfast consisted of 100 g of bread, 20 g of butter, 35 g of cucumber, 2 boiled egg and 200 ml of milk. Subjects did not eat for 4 h after receiving drugs, and then took food and drink *ad libitum*. Urine samples were collected 0.5, 1.5, 2.5, 3.5, 4.5, 5.5, 6.5, 8, 10, 12, 15 and 24 h after administration, the volume of urine was measured and an aliquot was stored frozen at \(-15^\circ\text{C}\) until assayed.

**Assay** — Total I (free and alkali-labile conjugated I) in the urine was determined fluorometrically\(^9,10\) after hydrolysis of conjugated I.

A sample of 0.5 ml of the urine was mixed with 0.5 ml of 0.1 N NaOH in a test tube and heated in a water bath at 100°C for 30 min. The solution was then cooled to room temperature, mixed with 1 ml of 1 N H₂SO₄ and extracted with 8 ml of carbon tetrachloride. Then 6 ml of the organic phase was re-extracted with 6 ml of 0.1N NaOH and 5 ml of the aqueous phase was mixed with 1.2 ml of acetic acid and 0.5 ml of 1% potassium dichromate in another test tube. The solution was left for 30 min at room temperature and then extracted with 6 ml of carbon tetrachloride. Then 5 ml of organic phase was transferred to another test tube containing 0.1 ml of 50% trichloroacetic acid in carbon tetrachloride. Fluorescence was measured using excitation and

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**FIG. 1. Urinary Excretion Rate-Time (Upper) and Cumulative Amount of Excretion-Time Curves (Below) of Total I**

- ●, a I capsule administered in the fasting state.
- ■, a I capsule co-administered with III gel in the fasting state. ▲, a I capsule administered in the nonfasting state. ○, a II tablet administered in the fasting state. □, a II tablet administered in the nonfasting state.
emission wave lengths of 366 and 440 nm, respectively.

Statistical Analyses — The excretion rate of total I at the midpoint \( V_r \) between the sampling times, the cumulative amount of urinary excretion in 24 h \( E_{24} \) and the infinity \( E_\infty \) calculated,\(^1\) the maximum excretion rate \( V_{\text{max}} \), the time of the maximum excretion rate \( T_{\text{max}} \) and the lag time for excretion of I \( T_{\text{lag}} \) were compared using ANOVA\(^1\) to investigate the bioequivalence of the five treatments. \( T_{\text{lag}} \) was obtained by extrapolation on the excretion rate-time curves. All values except \( T_{\text{max}} \) and \( T_{\text{lag}} \) were corrected for the contents of I in a tablet or capsule. When necessary, a multiple range test by the l.s.d. (least significant difference) method\(^2\) was used for pair-wise comparison of the means of the five treatments.

Dissolution Rate — The dissolution rates of I from the I capsule and tablet were determined by the oscillating basket,\(^3\) rotating basket and paddle methods (USP XIX) using 900 ml of dissolution medium. The tests were done under following two different conditions.

Constant pH: The first fluid of disintegration test (JP IX) adjusted to pH 7.6 with trisodium phosphate 12 hydrate was used.

Successive pH increase: The first fluid (JP IX) (pH 1.2) was used for the first 30 min, and then 12 g of trisodium phosphate 12 hydrate was added to increase the pH to 6.4. After 90 min, 6 g of the same salt was again added to increase the pH to 7.6.

The I concentration in the stream pumped (3 ml/min) through the flow cell was monitored at 345 nm, where the absorbance at 100% of I dissolved was nearly 0.76.

RESULTS AND DISCUSSION

Bioavailability

Fig. 1 shows average excretion rate-time and cumulative amount of urinary excretion-time profiles of total I after each treatment. The results of ANOVA and the multiple range test are summarized in Table I. Treatment A (I capsule administered in the fasting state) gave the highest values of the average \( V_{0.25} \), \( V_{1.0} \) and \( V_{\text{max}} \), and the shortest values of \( T_{\text{lag}} \) and \( T_{\text{max}} \), though none of the differences between these values and those after treatment B (I capsule coadministered with III gel in the fasting state) were significant except that of \( V_{0.25} \) \((p < 0.05)\).

### Table I. Bioavailability Parameters of I after Each Treatment

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Treatment</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>
<th>( \text{p} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>( V_{0.25} ) (mg/h)</td>
<td></td>
<td>0.691</td>
<td>0.332</td>
<td>0.009</td>
<td>0.034</td>
<td>0.023</td>
<td>(&lt; 0.01)</td>
<td>( A &gt; B &gt; D &gt; E &gt; C )</td>
<td></td>
</tr>
<tr>
<td>( V_{1.0} )</td>
<td></td>
<td>5.060</td>
<td>3.846</td>
<td>0.810</td>
<td>0.344</td>
<td>0.253</td>
<td>(&lt; 0.01)</td>
<td>( A &gt; B &gt; C &gt; D &gt; E )</td>
<td></td>
</tr>
<tr>
<td>( V_{2.0} )</td>
<td></td>
<td>3.644</td>
<td>4.203</td>
<td>2.911</td>
<td>0.488</td>
<td>0.718</td>
<td>(&lt; 0.01)</td>
<td>( B &gt; A &gt; C &gt; E &gt; D )</td>
<td></td>
</tr>
<tr>
<td>( V_{5.0} )</td>
<td></td>
<td>2.548</td>
<td>2.643</td>
<td>3.289</td>
<td>0.432</td>
<td>0.759</td>
<td>(&lt; 0.01)</td>
<td>( C &gt; B &gt; A &gt; E &gt; D )</td>
<td></td>
</tr>
<tr>
<td>( V_{6.0} )</td>
<td></td>
<td>1.944</td>
<td>2.000</td>
<td>2.996</td>
<td>0.407</td>
<td>0.513</td>
<td>N.S.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( V_{\text{max}} ) (mg/h)</td>
<td></td>
<td>1.512</td>
<td>1.749</td>
<td>2.820</td>
<td>0.453</td>
<td>0.416</td>
<td>N.S.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( T_{\text{lag}} ) (h)</td>
<td></td>
<td>1.029</td>
<td>1.325</td>
<td>1.458</td>
<td>0.368</td>
<td>0.407</td>
<td>N.S.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( T_{\text{max}} ) (h)</td>
<td></td>
<td>1.029</td>
<td>1.325</td>
<td>1.458</td>
<td>0.368</td>
<td>0.407</td>
<td>N.S.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\( a) \) The mean values for treatments not underscored by the same line differ significantly.
The values of $V_{0.25}$, $V_{1.0}$ and $T_{lag}$ after treatment C (I capsule administered in the nonfasting state) differed statistically from those after treatments A and B, but $E_{24}$ and $E_{\infty}$ were almost the same after these treatments.

On the other hand, the bioavailability was very low in treatments D and E, in which a II tablet was administered in the fasting and nonfasting states, respectively, compared with those of a I capsule, as shown by the fact that the differences in $V_{0.25}$, $V_{1.0}$, $V_{2.0}$, $V_{3.0}$, $V_{\text{max}}$, $E_{24}$ and $E_{\infty}$ were significant. $V_{\text{max}}$ and $E_{\infty}$ after a II tablet were only less than 20 and 30% of those after a I capsule. No differences were detected between the bioavailability of treatments D and E.

I was absorbed rapidly from the I capsule used in this work, though previously we found that some I capsules had low bioavailabilities. Co-administration with III gel did not affect the absorption of I from the I capsule. Concomitant intake of food retarded I absorption to some degree, but did not reduce the bioavailability. On the other hand, the bioavailability of I from the II tablet was extremely low, and did not increase even when the tablet was given 30 min after a standard breakfast.

**Dissolution Rate**

Fig. 2 shows the dissolution rates of I from the I capsule and II tablet determined by the oscillating basket method. The dissolution of I from the II tablet was much slower than that from the I capsule both at constant pH (pH 7.6) and in the successive pH increase method. The dissolution rate of I from the II tablet decreased with time after about 10% of I had dissolved, and only about 20 to 30% of I dissolved within 3 h. In contrast with the II tablet, once dissolution from the I capsule had begun, I dissolved completely within 10 min. The rotating basket and paddle methods also showed that the dissolution rate of I from the II tablet was slow and incomplete (Table II).

Winder et al. reported that after oral administration of 200 mg of $^{14}$C labelled I, 51% of the administered radio activity was accounted for in the urine, and that nearly equal amounts of conjugated I (18%) and partly conjugated 4'-hydroxy metabolite (23%) were excreted in 72 h with smaller amounts of 5-hydroxy (3%) and 4', 5-dihydroxy (7%) metabolites. They showed that I (9%) and mono- and di-hydroxy metabolites (27%) were also recovered in the feces. In this study, 20% of the I administered was recovered in free and conjugated forms in 24 h after treatments A, B and C, and the total I excreted was recovered in 24 h ($E_{24}/E_{\infty} > 0.98$). With the II tablet, nearly the same values of

![Dissolution Rate Graph](image)

**FIG. 2. Dissolution Rates of I from the I Capsule and II Tablet determined by the Oscillating Basket Method**

- ●, I capsule at pH 7.6. ○, I capsule by the successive pH increase method.
- ■, II tablet at pH 7.6. □, II tablet by the successive pH increase method.

**TABLE II. % Dissolution of I from the II Tablet in 3 h (n=3)**

<table>
<thead>
<tr>
<th>Dissolution method</th>
<th>Constant pH (7.6)</th>
<th>Successive pH increase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rotating basket</td>
<td>14.3%</td>
<td>16.8%</td>
</tr>
<tr>
<td>Paddle</td>
<td>15.6%</td>
<td>16.4%</td>
</tr>
<tr>
<td>Oscillating basket</td>
<td>32.5%</td>
<td>23.4%</td>
</tr>
</tbody>
</table>
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were obtained, though only 5% of the I was recovered as total I in 24 h after its oral administration. So the amount of I absorbed from the II tablet was only one-third or one-fourth of that from the I capsule.

As mentioned above, I sometimes causes severe gastric distress and irritation when given in multiple doses, and in such cases it is frequently administered concomitantly with antacid or a meal. The effects of food on drug bioavailability have been studied by many authors. Food is known to retard the absorption of drugs, mainly by reducing the gastric emptying rate. In case of I, a standard meal retarded the absorption from a I capsule, but did not reduce the extent of bioavailability at all. Thus the reduced absorption rate may be due to reduction of the gastric emptying rate.

On the other hand, food is also known to enhance drug bioavailability. The absorption of a drug having low solubility in water or gastric fluid such as griseofulvin is enhanced by food intake, because bile increased its solubility. But the low I bioavailability from the II tablet, developed for the purpose of reducing the severe gastric side effects of I, was not increased by food intake, probably because of the very low solubility of I and the strong binding of I in the II complex. The very slow release of I from II may also due to formation of an insoluble film of aluminum on the surface of the solid, as suggested in the case of aspirin aluminum by Levy and Procknel.

Antacids containing aluminum ion affect drug absorption, reducing the gastric emptying rate, owing to their relaxing effect on gastric muscle. But in this study, III gel did not affect the bioavailability of I from a I capsule. This may be because the smaller dose of III (0.3 g), which is the minimum of the usual dose, was given than that (3 doses of 0.3 to 0.7 g) used in the study by Hurwitz. Thus administration of food or antacid to prevent side effects does not seem to affect the bioavailability of I from I capsules.

It is concluded that the bioavailability of I from the II tablet, which was developed to reduce the severe gastric side effects of I, is very low and is not increased by food intake. On the other hand, food intake only retarded I absorption from the I capsule slightly, probably by reducing the gastric emptying rate, and III gel had little effect on the absorption of I. These results suggested that I should be administered immediately after food or antacid intake, which do not affect its bioavailability but reduce gastric distress and irritation.

REFERENCES


