BIOPHARMACEUTICAL STUDIES ON HYDANTOIN DERIVATIVES. IV. 1) FACTORS AFFECTING BIOAVAILABILITY OF 5,5-DIPHENYLHYDANTOIN IN DOG 2)

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Several factors affecting the bioavailability of 5,5-diphenylhydantoin (I) and its sodium salt (I-Na) were examined in dogs in relation to meal and following results were obtained.

1) The bioavailability of I was not appreciably affected by the volume of co-administered water in the range of 30—120 ml.
2) The bioavailability of I was most excellent when I was administered 0.5 h after meal. Food intake 0.5 h after drug administration enhanced appreciably the bioavailability, but that 2 h after drug administration did hardly affect the bioavailability.
3) The extent of bioavailability of I-Na was almost 100% of the dose in the range of 100—400 mg/dog when it was administered 0.5 h after meal. While, when I-Na was administered in the fasting state, the extent of bioavailability was about 60% of the dose.
4) Food-induced enhancement of the bioavailability of I was independent of the food constituents.
5) The bioavailability of I was increased about 1.5-fold and 2-fold with 10-fold increase in the specific surface area of I, in the nonfasting and the fasting states, respectively.
6) In the experiments using the dogs with the chronically implanted fistula in the common bile duct, it was found that the bile was not a major factor contributing to the food-induced enhancement of the bioavailability of I.
7) There was a good correlation between the bioavailability of I in dog and that in man.

Keywords— 5,5-diphenylhydantoin; plasma concentration; bioavailability; dog; man; fluid volume; food; particle size; bile; bile duct fistula

5,5-Diphenylhydantoins are scarcely soluble in water 3) and the dissolution rate in the gastrointestinal tract is the rate-determining step in the bioavailability. 4) This may be a factor which makes it difficult to predict the dosage regimen of 5,5-diphenylhydantoin needed to achieve a desired plasma concentration for seizure control, 5) even though the therapeutic and toxic ranges of the plasma concentration were defined. 6) Therefore, physical and pharmaceutical means of improving the dissolution and hence bioavailability of 5,5-diphenylhydantoin were attempted. 7)

On the other hand, the bioavailability may be influenced by the physiological factors, i.e., gastrointestinal motility, stomach emptying, secretion of digestive fluids and bile flow, etc., which are directly concerned with food ingestion. 8) It is said that meal enhances the bioavailability of 5,5-diphenylhydantoin in man 9) and in dog, 10) but it is not yet clear as to why the effect of meal varies with the particle size of the materials and with the time of administration in relation to meal. It is considered that the bile flow plays an important role in the enhancing effect of meal on the bioavailability of slightly water-soluble drugs, 11) but it is not yet demonstrated.

Hence, an investigation was undertaken to
determine the effect of various factors influencing the bioavailability of 5,5-diphenylhydantoins in relation to meal, i.e., volume of water taken with the drug, time of dosage administration, dietary components, specific surface area of the materials, and dose. Another object of this study is to determine to what extent the bile flow contributes to the food-induced enhancement of bioavailability. For this purpose, physiologically normal dogs with chronically implanted fistula in the common bile duct were newly prepared. Furthermore, the aim of this study is to find the correlation of the bioavailability in dog with that in man.

EXPERIMENTAL

Materials — The materials used were as follows: 5,5-Diphenylhydantoin (I), seven raw materials of I with different specific surface areas of 5.643, 1.786, 1.076 and 0.530 m²/g and different particle sizes of about 10, 70 and 500 μm which were prepared under different precipitation conditions, and unless otherwise stated the material of the specific surface area of 1.786 m²/g was used; sodium 5,5-diphenylhydantoin (I-Na); 1-benzenesulfonyl-5,5-diphenylhydantoin (II) of the specific surface area of 3.410 m²/g; sodium 1-benzenesulfonfyl-5,5-diphenylhydantoin trihydrate (II-Na).

Measurement of Specific Surface Area — The specific surface area of materials was determined by analyzing the data obtained in low-temperature nitrogen adsorption experiments with Sibata P-600 Surface Area Apparatus, according to BET equation.¹²

Experiments in Dogs — Cross-over tests were carried out on male beagle dogs weighing about 15 kg at 2-week intervals.

Oral Administration: Each material was loaded into a glass tube connected to the upper end of a cannula and was poured with 60 ml of water into the stomach of dogs fasted overnight prior to the experiments. Doses used were as follows: for I, 200 mg; for I-Na, equivalent in amount to 100—400 mg of I; for II, 450 mg.

Intravenous Administration: Solution of each material was injected into the brachial vein of dogs fasted overnight prior to the experiments. Doses used were as follows: for I-Na, equivalent in amount to 100 mg of I in 10 ml of water; for II-Na, equivalent in amount to 100 mg of II in 10 ml of an aqueous solution of propylene glycol–ethanol–water(4:1:5, v/v).

Unless otherwise stated, no food was given for 8 h after drug administration and heparinized blood samples were taken at preselected time intervals up to 24 h. Plasma was separated within 30 min by centrifugation.

Determination of I and II in Plasma — Plasma concentrations of I and II were determined by gas chromatography.⁴

Determination of I in Feces — To feces collected for 56 h from dogs receiving I in a 3-l polyethylene vessel, 1 l of 0.1 N NaOH containing specified amount of 5-p-methylphenyl-5-phenylhydantoin as an internal standard was added. The feces suspension was adjusted to pH 11.5 by adding NaOH. The vessel was vigorously shaken for 30 min and I was completely dissolved. The mixture was centrifuged and 1 ml of the supernatant was analyzed according to the identical procedure used for plasma.

Evaluation of Bioavailability — The rate and extent of bioavailability of I and II were calculated from the plasma concentrations according to the previously reported procedure.⁴

Test Diets — The standard diet is a mixture of 350 g of dog food CD-1 (Nippon Clea Co., Ltd.) and 20 g of skim milk, swelled with 350 ml of water. The effect of diet constituents on the bioavailability was examined with the special diets the constituents of which are summarized in Table I. Unless otherwise stated, the effect of meal was studied with the standard diet.

Surgical Operation for Chronic Biliary External Fistula — Several reports on the biliary fistula in dogs are available,¹³ but in these reports the operated dogs had not necessarily the physiologically normal or intact enterohepatic biliary system. It is also said that the surgical operation causes changes in the pharmacokinetics.¹⁴ Hence, a new chronic biliary external fistula was prepared in male beagle dogs, according to the scheme shown in
TABLE I. Compositions of Diets Used in Studies on Effect of Meal on Bioavailability

<table>
<thead>
<tr>
<th></th>
<th>Water</th>
<th>Protein</th>
<th>Fat</th>
<th>Carbohydrate</th>
<th>Ash</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard meal</td>
<td>377.09</td>
<td>94.46</td>
<td>21.20</td>
<td>197.69</td>
<td>29.57</td>
<td>720</td>
</tr>
<tr>
<td>Hight fat meal</td>
<td>366.6</td>
<td>9.24</td>
<td>22.55</td>
<td>130.49</td>
<td>1.12</td>
<td>530</td>
</tr>
<tr>
<td>High carbohydrate meal</td>
<td>460.84</td>
<td>15.36</td>
<td>1.00</td>
<td>170.84</td>
<td>1.96</td>
<td>650</td>
</tr>
<tr>
<td>High protein meal</td>
<td>471.64</td>
<td>96.82</td>
<td>1.41</td>
<td>92.29</td>
<td>7.84</td>
<td>670</td>
</tr>
</tbody>
</table>

Fig. 1.
The common bile duct was catheterized with the silicon tubes T₂ and T₂' (3 mm o.d., Yamada Rubber Co., Ltd.) which were connected at point B and B' to the silicon tubes T₁ and T₁' (Technicon 110 116-0536-18, Fujisawa Supply Co., Ltd.) passed through the abdominal wall, on the inner and outer sides of which the silicon rings (10 mm o.d.) were placed over the tubes to secure them. The inside of the silicon tubes at the abdominal wall were reinforced with the polyethylene tube (Hibiki Co., Ltd.). Each connection of the silicon tubes was made with the polyethylene tubes.

The enterohepatic biliary circuit was prepared by joining the external sections of the tubes T₁ and T₁' at point A, through which the bile returns to the common bile duct. The situation is termed the bile return state. While, for the collection of the bile, the external tip of the tube T₁' was closed with a plastic plug and that of the tube T₁ was joined to a polyethylene vessel, into which the bile was drained. The situation is termed the bile collection state. In this operation, inasmuch as the cannulas were placed only in a part of the common bile duct, the physiological functions of all the organs consisting the enterohepatic biliary system in the operated dogs are quite normal. With this model it has become feasible not only to determine the degree of contribution of the bile to the effect of meal on the bioavailability, but also to investigate the enterohepatic recirculation of drugs and the metabolites. A picture of an operated dog is shown in Fig. 2.

The experiments on the bioavailability in the operated dogs were undertaken after a recovery period of 10 d from the time of surgery. In order to explore the effect of operation on the pharmacokinetics of I, plasma concentrations of I were measured following intravenous injection of I to dogs before and after the operation. The apparent volume of distribution, $V_d$, and the first order rate constant of elimination, $K_{el}$, were estimated from the plasma data and summarized in Table II.
There was no significant difference in both the $V_d$ values and the $K_{el}$ values between before and after operation.

*Experimentals in Human Volunteers* — The subjects were 6 healthy male volunteers, 42 to 54 years old and weighing 57 to 78 kg. They received extensive information about the study, and gave written consent to participation in it. They were fasted overnight prior to experiments. A single 200 mg of I was orally administered with 200 ml of water 0.5 h after a breakfast of 2 slices of buttered toast, a boiled egg, and a cup of coffee. Plasma specimens were collected 2, 4, 6, 8, 24, and 48 h thereafter. No food was given for 4 h after drug administration. The experiments were carried out according to a Latin Square design, allowing a 1-week interval between drug administrations.

**RESULTS AND DISCUSSION**

*Effect of Volume of Co-administered Water on the Bioavailability of I in Dogs*

Mean plasma concentrations of I after oral administration of I with 30, 60, or 120 ml of water to fasted dogs are summarized in Fig. 3. Plasma concentrations of I during the first 2 h tended to be lower after dosing with 30 ml of water than after dosing with 60 or 120 ml of water, but the differences were not significant. The areas under the plasma concentration-time curves were nearly identical in all three treatment conditions. The results indicate that the initial

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**FIG. 2. A Surgically Operated Dog with Chronic Fistula in the Common Bile Duct**

The arrow shows the external portion of the fistula.

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**TABLE II. **Pharmacokinetic Data of I before and after Operation

<table>
<thead>
<tr>
<th>Dog</th>
<th>Weight kg</th>
<th>$V_d$ 1/kg</th>
<th>$K_{el}$ h$^{-1}$</th>
<th>Biological half-life h</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 d before operation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>13.0</td>
<td>1.44</td>
<td>0.215</td>
<td>3.23</td>
</tr>
<tr>
<td>2</td>
<td>12.5</td>
<td>1.47</td>
<td>0.199</td>
<td>3.48</td>
</tr>
<tr>
<td>3</td>
<td>12.5</td>
<td>1.15</td>
<td>0.232</td>
<td>2.98</td>
</tr>
<tr>
<td>Mean</td>
<td>12.7</td>
<td>1.35</td>
<td>0.215</td>
<td>3.23</td>
</tr>
<tr>
<td>SE</td>
<td>0.2</td>
<td>0.10</td>
<td>0.010</td>
<td>0.14</td>
</tr>
<tr>
<td>30 d after operation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>13.0</td>
<td>1.39</td>
<td>0.222</td>
<td>3.12</td>
</tr>
<tr>
<td>2</td>
<td>15.0</td>
<td>1.27</td>
<td>0.219</td>
<td>3.17</td>
</tr>
<tr>
<td>3</td>
<td>13.0</td>
<td>1.39</td>
<td>0.178</td>
<td>3.89</td>
</tr>
<tr>
<td>Mean</td>
<td>13.7</td>
<td>1.35</td>
<td>0.206</td>
<td>3.39</td>
</tr>
<tr>
<td>SE</td>
<td>0.7</td>
<td>0.04</td>
<td>0.014</td>
<td>0.25</td>
</tr>
</tbody>
</table>
rate of bioavailability may be reduced when I is administered with a small volume of water, but the extent of bioavailability is essentially independent of volume of water.

**Effect of Time of Administration in Relation to Meal on the Bioavailability of I in Dogs**

Mean plasma concentrations of I after oral administration of I at different times in relation to meal, together with statistical comparisons, are summarized in Table III and in Fig. 4. The rates and the extents of bioavailability are shown in Fig. 5. When I was administered 0.5 h after meal, the plasma concentrations of I were extremely high over entire period of sampling compared with those for other treatments, the bioavailability being the best. Food intake 2 h after administration of I did not significantly affect the bioavailability. Food intake 0.5 h after administration of I resulted in the intermediate bioavailability and the rapid rise in the plasma concentration after 1 h represents clearly the effect of meal.

**TABLE III. Effect of Time of Administration of I in Relation to Meal on the Bioavailability of I**

<table>
<thead>
<tr>
<th>Time of drug administration</th>
<th>0.5 h after meal</th>
<th>0.5 h before meal</th>
<th>2 h before meal</th>
<th>In the fasting state</th>
<th>Paired t test</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>1.53±0.13</td>
<td>0.87±0.05</td>
<td>0.87±0.05</td>
<td>0.74±0.16</td>
<td>A&gt;B&gt;C,D</td>
</tr>
<tr>
<td>1 h</td>
<td>3.46±0.26</td>
<td>1.79±0.07</td>
<td>1.39±0.08</td>
<td>1.16±0.13</td>
<td>A&gt;B&gt;C,D</td>
</tr>
<tr>
<td>2 h</td>
<td>4.83±0.38</td>
<td>3.32±0.19</td>
<td>1.77±0.09</td>
<td>1.42±0.18</td>
<td>A&gt;B&gt;C,D</td>
</tr>
<tr>
<td>4 h</td>
<td>4.23±0.46</td>
<td>3.10±0.20</td>
<td>1.66±0.27</td>
<td>1.37±0.24</td>
<td>A&gt;B&gt;C,D</td>
</tr>
<tr>
<td>6 h</td>
<td>3.07±0.41</td>
<td>2.46±0.26</td>
<td>1.27±0.17</td>
<td>1.11±0.14</td>
<td>A&gt;B&gt;C,D</td>
</tr>
<tr>
<td>8 h</td>
<td>2.37±0.32</td>
<td>2.00±0.22</td>
<td>1.06±0.15</td>
<td>0.85±0.05</td>
<td>A&gt;B&gt;C,D</td>
</tr>
<tr>
<td>Plasma concentration of I, μg/ml</td>
<td>4.90±0.38</td>
<td>3.40±0.17</td>
<td>1.95±0.23</td>
<td>1.47±0.22</td>
<td>A&gt;B&gt;C,D</td>
</tr>
<tr>
<td>C_{max} a) μg/ml</td>
<td>2.33±0.33</td>
<td>2.67±0.42</td>
<td>2.33±0.33</td>
<td>2.67±0.42</td>
<td>NSD c)</td>
</tr>
<tr>
<td>Extent of bioavailability, % of dose</td>
<td>73.2±7.4</td>
<td>55.2±3.6</td>
<td>30.2±3.8</td>
<td>24.9±2.4</td>
<td>A&gt;B&gt;C,D</td>
</tr>
</tbody>
</table>

Data represent mean ± SE for 6 animals.

a) Peak plasma concentration.
b) Time to reach peak plasma concentration.
c) Not significantly different.
d) Significant at p<0.05.
e) Extent of bioavailability up to 8 h after oral administration.
For each treatment, the peak plasma concentration of I occurred at approximately 2.5 h after administration and the absorption lasted for about 5 h. But the rate and the extent of bioavailability are significantly dependent of time of administration in relation to meal.

As can be seen in Fig. 6, the enhancing effect of meal on the bioavailability was also observed for II which is slightly soluble in water. The extent of bioavailability up to 8 h after administration was 70% of the dose when II was administered 0.5 h after meal, and 35% of the dose in the fasting dogs.

**Effect of Dietary Constituents on the Bioavailability of I in Dogs**

The extents of bioavailability following oral administration of I 0.5 h after various test meals *i.e.* high-carbohydrate, high-fat, and high-protein meals in lieu of the standard meal are summarized in Fig. 7. There was no significant difference in the extent of bioavailability among all treatments. The results indicate that the enhancing effect of

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**FIG. 4. Mean Plasma Concentration–Time Curves of I Following Oral Administration of 200 mg of I with 60 ml of Water to Dogs 0.5 h after Meal (○), 0.5 h before Meal (△), 2 h before Meal (●), or in the Fasting State (□).

Each point is the mean ± SE for 6 animals. Each arrow indicates the time of meal.**

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**FIG. 6. Mean Plasma Concentration–Time Curves of II Following Oral Administration of 450 mg of II with 60 ml of Water to Dogs 0.5 h after Meal (●) or in the Fasting State (○).

Each point is the mean ± SE for 6 animals.**

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**FIG. 5. Mean Rates (Thin Line) and Extents (Thick Line) of Bioavailability of I Following Oral Administration of 200 mg of I with 60 ml of Water to Dogs 0.5 h after Meal (——), 0.5 h before Meal (———), 2 h before Meal (— — — — ), or in the Fasting State (——— —).

Vertical bracketed lines at 8 h represent standard error of the mean.**
meal on the bioavailability of I is not dependent of kinds and constituents of diet. Similarly, it is known that changes in dietary macronutrient composition have no significant effect on the pharmacokinetics of I in man.\textsuperscript{9,15}

**Effect of Specific Surface Area on the Bioavailability of I in Dogs**

The extents of bioavailability of I up to 8 h after oral administration of I with different specific surface areas to the fasted dogs and to the nonfasted dogs (0.5 h after meal) are summarized in Fig. 8. An approximately linear relationship existed between the extent of bioavailability and the logarithm of the specific surface area, in each fasting state and nonfasting state, 10-fold increase in the specific surface area resulting in about 2-fold increase in the extent of bioavailability in the former and 1.5-fold increase in the latter. When I with the specific surface area of 5.643 m\textsuperscript{2}/g was administered to the nonfasted dogs, the extent of bioavailability was about 90% of the dose. A similar semilogarithmic relationship with samples of griseofulvin of specific surface area of 0.36−2.43 m\textsuperscript{2}/g in man has been reported, in which 4-fold increase in the specific surface area resulted in about 2-fold increase in absorbability.\textsuperscript{16} But in this case, nothing was mentioned on meal.

**Effect of Dose and Meal on the Bioavailability of I-Na in Dogs**

Plasma concentrations of I after oral administration of I-Na equivalent in amount to 100, 200, and 400 mg of I to the nonfasted dogs (0.5 h after meal) and to the fasted dogs are summarized in Fig. 9. The relationship between the dose and the extent of bioavailability up to 8 h after administration is shown in Fig. 10. When I-Na was administered in the nonfasting state, the extent of bioavailability was almost 100% of the dose in the range of 100 to 400 mg. Although mean peak plasma concentration of I was nearly proportional to the dose, the time to reach the peak concentration increased from 2 h for 100 and 200 mg doses to 4 h for the 400 mg dose. The plasma concentrations of I during the first 1 h after oral dosages of 200 mg and 400 mg in the nonfasted dogs were approximately equal, suggesting that during the initial period the rate of bioavailability is saturated at the dose more than 200 mg.

![Graph showing bioavailability](image_url)

**FIG. 7. Extents of Bioavailability up to 8 h Following Oral Administration of 200 mg of I with 60 ml of Water to Dogs 0.5 h after Various Test Meals The data are the mean ± SE for 3 animals.**

![Graph showing relationship between specific surface area and bioavailability](image_url)

**FIG. 8. Relationship between Specific Surface Area of I and Extent of Bioavailability up to 8 h after Oral Administration to Dogs**

- \(\bullet\), administered 0.5 h after meal.
- \(\circ\), administered in the fasting state.

Each point is the mean ± SE for 6 animals.
When I-Na was administered in the fasting state, the plasma concentrations of I were significantly lower than those in the nonfasting state over entire sampling times, the extent of bioavailability being about 60% of the dose. But the time to reach the peak concentration for the 200 mg dose was about 2 h, irrespective of whether meal was taken or not. Although I-Na is soluble in water, once dissolved I-Na in the empty stomach may again in part precipitate as the free form, I. On the other hand, when I-Na is administered after meal, precipitation of I in the stomach should be inhibited due to the diffusion of the dissolved I-Na into the chyme of gut contents with the aid of secretion of the digestive fluids and the intense gastrointestinal motility which are caused by meal. These may explain the difference in the extent of bioavailability between the fasting state and the nonfasting state.

**Effect of Bile on the Bioavailability of I in Dogs**

The plasma concentrations of I following oral administration of I together with 60 ml of water or 60 ml of the bile to the fasting dogs are summarized in Fig. 11. The bile used was collected from the operated dogs with the chronic biliary external fistula.

When I was administered with the bile, the plasma concentrations of I were about 2 times
higher than those after dosing with water over the entire period, the differences being significant at each sampling time. It is clear that the bile enhanced the bioavailability of I, but the enhancing effect was less than that of meal.

**Contribution of Bile Flow to the Enhancing Effect of Meal on the Bioavailability of I in Dogs**

In view of the fact that meal causes the flow of the bile into the duodenum\(^\text{17}\) and that the bile increased the bioavailability of I, it is presumed that the bile is concerned in the enhancing effect of meal on the bioavailability of I. If the effect of meal on the bioavailability of I is attributed solely to the function of the bile, no effect ought to be observed when the bile flow into the duodenum is stopped. In order to make this point clear, the effect of meal on the bioavailability of I was examined by applying the operated dogs with the chronic biliary external fistula.

The plasma concentrations of I following oral administration of I to the operated dogs under various states in relation to meal and to the bile flow are summarized in Fig. 12. The rate and extents of bioavailability of I are shown in Fig. 13. The extents of bioavailability of I under the bile return state were 85% of the dose when I was administered 0.5 h after meal and 26% of the dose when it was administered in the fasting state, these being in fair agreement with those in the nonoperated dogs described above. The results together with the data in Table I justify that the surgical operation causes no change in the pharmacokinetics of I in the body. On the other hand, when I was administered 0.5 h after meal under the bile collection state, the extent of bioavailability was 74% of the dose, this being more comparable to the bioavailability attained in the nonfasting state under the bile return state rather than that attained in the fasting state under

**FIG. 12. Mean Plasma Concentration - Time Curves of I Following Oral Administration of 200 mg of I with 60 ml of Water to the Operated Dogs 0.5 h after Meal under the Bile — Return State (●), 0.5 h after Meal under the Bile — Collection State (△), or in the Fasting State under the Bile — Return State (○).

Each point is the mean ± SE for 3 animals.**

**FIG. 13. Mean Rates (Thin Line) and Extents (Thick Line) of Bioavailability of I Following Oral Administration of 200 mg of I with 60 ml of Water to the Operated Dogs 0.5 h after Meal under the Bile — Return State (-----), 0.5 h after Meal under the Bile — Collection State (-----), or in the Fasting State under the Bile — Return State (-------).

Vertical bracketed lines at 8 h represent standard error of the mean.**
the bile return state. It is clear that I is well absorbed when it is administered after meal even in the absence of the bile flow into the duodenum.

These results suggest that the bile may contribute in part to the enhancing effect of meal on the bioavailability but many other factors caused by meal, i.e., the intense gastrointestinal motility, secretion of the digestive fluid, slow gastric emptying, etc. may simultaneously participate in the enhancing effect on the bioavailability, probably due to the increase in dispersion and dissolution rate of I in the guts.

Relationship between the Extent of Bioavailability and the Amount Excreted in Feces

The amounts of I excreted in feces for 56 h following oral administration of I or I-Na to dogs were also measured, along with the plasma concentrations. As can be seen in Table IV, the sum of the amount of I excreted in feces and the extent of bioavailability of I calculated pharmacokinetically from the plasma concentrations was nearly equal to the administered dose in each case. In experiments using dogs with the chronic biliary external fistula, the amount of I excreted in the bile was found to be 1–3% of the extent of bioavailability, indicating that the enterohepatic circulation participates to a lesser extent in the pharmacokinetics of I. The results suggest that the pharmacokinetic evaluation of the bioavailability is actually valid.

Relationship between the Bioavailability in Dog and That in Man

The results mentioned above shed light on factors which influence the bioavailability of I in dog in relation to meal. On the other hand, it is essential to clarify how the bioavailability in dog correlates with that in man. Hence, plasma concentrations of I were measured following oral administration of I of 3 different particle sizes to dogs and to human subjects 0.5 h after meal. In order to estimate the bioavailability, the areas under the plasma concentration-time curves (AUC) and the peak plasma concentrations (Cmax) were calculated and plotted in Fig. 14 and Fig. 15, respectively. There was a good correlation in either AUC or Cmax between dog and man. These results indicate that the comparative bioavailability of I in man should be to some extent predictable from the data in dog.

Acknowledgement The clinical portion of this study was conducted under the direction of Masami Saito, M.D., Department of Neuropsychiatry, Kansai Medical University. The

<table>
<thead>
<tr>
<th>Dog No.</th>
<th>Drug</th>
<th>Dose $^a$</th>
<th>Extent of bioavailability $^c$</th>
<th>Amount of I excreted in feces $^d$</th>
<th>Total amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>I-Na</td>
<td>100</td>
<td>99.0</td>
<td>4.4</td>
<td>103.4</td>
</tr>
<tr>
<td>2</td>
<td>I-Na</td>
<td>100</td>
<td>95.7</td>
<td>6.1</td>
<td>101.8</td>
</tr>
<tr>
<td>3</td>
<td>I-Na</td>
<td>200</td>
<td>195.4</td>
<td>5.5</td>
<td>200.7</td>
</tr>
<tr>
<td>4</td>
<td>I-Na $^b$</td>
<td>200</td>
<td>28.3</td>
<td>145.0</td>
<td>177.3</td>
</tr>
<tr>
<td>5</td>
<td>I-Na $^b$</td>
<td>200</td>
<td>51.6</td>
<td>143.6</td>
<td>195.2</td>
</tr>
<tr>
<td>6</td>
<td>I-Na</td>
<td>400</td>
<td>366.1</td>
<td>16.0</td>
<td>382.1</td>
</tr>
</tbody>
</table>

$a$) Dose is expressed in amount of I.

$b$) I of large particle size (about 500 $\mu m$ in diameter) was used in this experiment.

c) Extent of bioavailability up to 8 h after oral administration.

d) Amount of I excreted in feces for 56 h after oral administration.
Effect of Meal on Bioavailability

FIG. 14. Relationship between AUC in Man and That in Dog Following Oral Administration of 200 mg of L of Various Particle Sizes

Mean particle size: ○, 10 μ m.
△, 70 μ m.
□, 500 μ m.

Each point is the mean±SE for 6 human subjects and for 6 animals. AUCs were calculated from plasma data for 0—48 h.

FIG. 15. Relationship between Cmax in Man and That in Dog Following Oral Administration of 200 mg of L of Various Particle Sizes

Mean particle size: ○, 10 μ m.
△, 70 μ m.
□, 500 μ m.

Each point is the mean±SE for 6 human subjects and for 6 animals.

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