Bioavailability of Griseofulvin from Tablets in Beagle Dogs and Correlation with Dissolution Rate and Bioavailability in Humans

NOBUO AOYAGI *, HIROYASU OGATA *, NAHOKO KANIWA *, MASANOBU KOIBUCHI *, TOSHIRO SHIBAZAKI *, AKIRA EJIMA *, NORIYASU TAMAKI †, HIDETAKA KAMIMURA ‡, YOSHIO KATOUGI †, and YUKIO OMI

Received July 31, 1981, from the *Division of Drugs, National Institute of Hygienic Sciences, 18-1, Kamiyoga 1-chome, Setagaya-ku, Tokyo 158, Japan; the †Yaizu Plant, Yamanouchi Pharmaceutical Co. Ltd., Ozumi-180, Yaizu-shi, Shizuoka-ken 425, Japan; and the ‡Institute of Research and Development, Yamanouchi Pharmaceutical Co. Ltd., 1-8, Azusawa 1-chome, Itabashi-ku, Tokyo 174, Japan.

Abstract The bioavailability of four griseofulvin tablets in beagle dogs, including an ultramicrsize tablet used previously in a human bioavailability study, was investigated on the basis of the plasma 6-demethylgriseofulvin concentration. The relations with the in vivo findings in humans and the in vitro dissolution rates also were examined. Contrary to the lower bioavailability of the ultramicrsize formulation in humans, it provided the best bioavailability in beagles. The microsize griseofulvin formulations showed similar in vivo results to those in humans. Poor correlation of in vivo parameters between humans and beagles was attributed to the discrepancy of the availability of the ultramicrsize formulation between the two species. The dissolution rates determined by the pretreatment method using plastic beads were correlated more with the in vivo findings than those determined by the other methods. Beagles were a useful animal model for bioavailability studies of certain griseofulvin formulations but not ultramicrsize ones.

Keyphrases Bioavailability—griseofulvin from tablets in beagle dogs, correlation with dissolution rate and bioavailability in humans

The bioavailabilities for four lots of griseofulvin tablets in humans have been reported previously, and the relations with in vitro dissolution rates have been discussed (1). Beagle dogs are often used as an animal model for bioavailability studies, but their suitability has not been clarified sufficiently. A good relation of penicillin bioavailability between humans and dogs was reported (2). Previous studies on bioavailability of diazepam formulations in humans and beagles revealed no good relations between the results from both species. The discrepancy was considered to be due to the differences of physiological states of the GI tract, especially of gastric emptying rate and GI transition time (3).

In the present study the bioavailability of griseofulvin from tablets in beagles was studied, and the relations with in vivo results in humans and in vitro dissolution rates were investigated.

EXPERIMENTAL

Formulations—Four lots of tablets containing 125 mg of griseofulvin employed in the human bioavailability study (1) were used. One formu-
Table I—Plasma Concentrations of Griseofulvin and 6-Demethylgriseofulvin Following Oral Administration of Formulation A to 12 Beagles

<table>
<thead>
<tr>
<th>In Vivo Parameter</th>
<th>Griseofulvin</th>
<th>Coefficient of Variation, %</th>
<th>6-Demethylgriseofulvin</th>
<th>Coefficient of Variation, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma Concentration µg/ml</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.5 hr</td>
<td>0.209 ± 0.202</td>
<td>97</td>
<td>1.559 ± 1.128</td>
<td>72</td>
</tr>
<tr>
<td>1</td>
<td>0.494 ± 0.481</td>
<td>97</td>
<td>2.562 ± 1.264</td>
<td>49</td>
</tr>
<tr>
<td>2</td>
<td>0.429 ± 0.298</td>
<td>70</td>
<td>2.059 ± 1.138</td>
<td>55</td>
</tr>
<tr>
<td>3</td>
<td>0.327 ± 0.196</td>
<td>60</td>
<td>1.519 ± 0.763</td>
<td>50</td>
</tr>
<tr>
<td>4</td>
<td>0.203 ± 0.116</td>
<td>57</td>
<td>1.092 ± 0.468</td>
<td>43</td>
</tr>
<tr>
<td>6</td>
<td>0.103 ± 0.036</td>
<td>35</td>
<td>0.843 ± 0.259</td>
<td>31</td>
</tr>
<tr>
<td>8</td>
<td>0.065 ± 0.033</td>
<td>51</td>
<td>0.753 ± 0.298</td>
<td>40</td>
</tr>
<tr>
<td>10</td>
<td>0.050 ± 0.036</td>
<td>73</td>
<td>0.544 ± 0.289</td>
<td>53</td>
</tr>
<tr>
<td>24</td>
<td>0.000 ± 0.010</td>
<td>333</td>
<td>0.127 ± 0.199</td>
<td>157</td>
</tr>
</tbody>
</table>

Cmax, µg/ml

0.626 ± 0.458 73 3.083 ± 1.114 36

Table II—Plasma Levels, Cmax, tmax, and AUC24 of 6-Demethylgriseofulvin Following Oral Administration of Four Lots of 125-mg Griseofulvin Tablets to Beagles

<table>
<thead>
<tr>
<th>In Vivo Parameter</th>
<th>Formulation</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>Result of ANOVA</th>
<th>Tukey’s Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma level, µg/ml</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.5 hr</td>
<td>1.559 ± 0.325</td>
<td>1.265 ± 0.290</td>
<td>0.640 ± 0.123</td>
<td>0.699 ± 0.229</td>
<td>p &lt; 0.05</td>
<td>A&gt;B&gt;D&gt;C</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>2.562 ± 0.365</td>
<td>1.857 ± 0.342</td>
<td>0.925 ± 0.112</td>
<td>1.222 ± 0.272</td>
<td>p &lt; 0.01</td>
<td>A&gt;B&gt;D&gt;C</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>2.059 ± 0.329</td>
<td>1.482 ± 0.314</td>
<td>0.977 ± 0.135</td>
<td>1.234 ± 0.105</td>
<td>p &lt; 0.01</td>
<td>A&gt;B&gt;D&gt;C</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>1.519 ± 0.220</td>
<td>1.170 ± 0.256</td>
<td>0.850 ± 0.138</td>
<td>0.951 ± 0.093</td>
<td>p &lt; 0.05</td>
<td>A&gt;B&gt;D&gt;C</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>1.092 ± 0.135</td>
<td>0.924 ± 0.199</td>
<td>0.845 ± 0.202</td>
<td>0.813 ± 0.136</td>
<td>NS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>0.843 ± 0.075</td>
<td>0.714 ± 0.135</td>
<td>0.540 ± 0.101</td>
<td>0.540 ± 0.098</td>
<td>NS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>0.753 ± 0.086</td>
<td>0.584 ± 0.110</td>
<td>0.434 ± 0.086</td>
<td>0.483 ± 0.081</td>
<td>NS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>0.544 ± 0.083</td>
<td>0.463 ± 0.102</td>
<td>0.282 ± 0.040</td>
<td>0.442 ± 0.102</td>
<td>NS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>0.127 ± 0.057</td>
<td>0.071 ± 0.017</td>
<td>0.077 ± 0.029</td>
<td>0.053 ± 0.015</td>
<td>NS</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Cmax, µg/ml

3.083 ± 0.321 2.340 ± 0.322 1.369 ± 0.156 1.749 ± 0.190 p < 0.01 A>B>D>C

tmax, hr

1.5 ± 0.2 1.3 ± 0.2 1.9 ± 0.5 1.7 ± 0.3 NS

AUC24, µg hr/ml

10.34 ± 1.38 12.86 ± 2.77 8.86 ± 1.05 10.62 ± 1.48 < 0.01 A>B>D>C

a The figures indicate means ± standard error. b NS: not significant. c Formulations underlined by a common line did not differ significantly (p < 0.05).
Dose–AUCm Relation—Three beagles were fasted overnight and given one and two tablets of Formulation C, corresponding to 125 and 250 mg of griseofulvin, respectively. The other procedures were the same as described for the bioavailability test.

Effects of Volume of Water Coadministered—Three formulations, including the ultramicrosize formulation, were used. Eight beagles were given a tablet with 30 and 200 ml of water in a crossover design. The other procedures were the same as described for the bioavailability test.

Assay—Griseofulvin and 6-demethylgriseofulvin in plasma were determined by GC (5).

RESULTS

Plasma Levels of Griseofulvin and 6-Demethylgriseofulvin—Table I shows the mean plasma griseofulvin and 6-demethylgriseofulvin concentrations after oral administration of Formulation A. The plasma griseofulvin concentrations were below one-fifth of those of 6-demethylgriseofulvin, and only a trace of griseofulvin was detected at 24 hr after administration of the drug. This can be attributed to the greater clearance of griseofulvin in dogs than in humans (6, 7), and hence, a considerable unabsorbed fraction of the dose administered orally will be converted to 6-demethylgriseofulvin by first-pass metabolism before reaching the blood circulation (8). The great clearance of griseofulvin probably leads to the greater bioavailability of griseofulvin in beagles was estimated on the basis of the plasma level of 6-demethylgriseofulvin.

Bioavailability—The relation of the griseofulvin dose and the AUCm of 6-demethylgriseofulvin is shown in Fig. 1. Large differences in the AUCm values among the beagles were found. With the high dose, the unabsorbed fraction of the drug may increase by being not fully dissolved in the GI tract.

Figure 2 shows the mean plasma level-time curves of 6-demethylgriseofulvin following oral administration of four formulations. Table II lists their mean values for in vivo parameters. The plasma levels of 6-demethylgriseofulvin at 24 hr were very low, so the AUCm can be considered as AUCm. Although the ultramicrosize formulation (A) showed relatively low bioavailability in humans (1), this formulation showed the highest values in the plasma concentrations, Cmax and AUC24, in beagles. The ratios of Cmax and AUC24 of the ultramicrosize formulation to those of Formulation B, which showed the highest availability of all microsize formulations, were 132 and 127%, respectively. Significant differences were found between Formulation A and two microsize formulations (C and D) in the plasma levels at earlier sampling times, Cmax and AUC24.

Correlation Between the Bioavailability and Dissolution Rates—The correlation coefficients between the in vivo parameters and in vitro dissolution rates (t50) determined by sink methods are shown in Table IV. The in vivo parameters are correlated more in the log-log and normal-reciprocal regressions with t50 determined by Method II (Table IV), in which the tablets were treated in 20 ml of water with plastic beads before the determination of dissolution rates.

Correlation Between Humans and Beagles—As shown in Table V, low correlation coefficients were found between humans and beagles. The poor correlations are attributed mainly to the discrepancy of the ultramicrosize formulation (A) between them. Figure 3 shows that the microsize formulations (B, C, D) showed a good relation (r = 0.976) in Cmax values between humans and beagles, which suggests that the bioavailabilities of microsize formulations can be evaluated in beagles instead of humans.

DISCUSSION

The in vivo findings in beagles did not correlate well with those in humans. The ultramicrosize formulation provided the best availability.
Antibradykinin Active Material in Aloe saponaria

AKIRA YAGI *, NOBUO HARADA †, HIDENORI YAMADA *, SHUICHI IWADARE ‡, and ITSUO NISHIOKA *

Received October 27, 1981, from the *Faculty of Pharmaceutical Sciences, Kyushu University, Maidashi, Higashi-ku, Fukuoka, Japan, and the †Banyu Pharmaceutical Co., Ltd., Nihonbashi hokcho, Chuo-ku, Tokyo, Japan. Accepted for publication December 31, 1981.

Abstract A material having antibradykinin activity on isolated guinea pig ileum was partially purified from the nondialysate of the pulp of Aloe saponaria by repetition of gel chromatography using a hydrophilic polyvinyl gel and dextran gels. From the results of amino acid and carbohydrate analyses, the antibradykinin-active material was estimated to be a glycoprotein. It was found that this material catalyzes the hydrolysis of bradykinin at pH 7.4. The results of peptide analysis using reversed-phase high-performance liquid chromatography coupled with amino acid analysis indicate that this glycoprotein cleaves the Gly^4-Phe^5 and Pro^3-Phe^4 bonds of the bradykinin molecule.

Keyphrases —Antibradykinin—active material in Aloe saponaria, guinea pig ileum, glycoprotein, high-performance liquid chromatography

Cardiac stimulant action of the constituents in the dialysate of the pulp from Aloe saponaria on isolated cardiac muscles has been reported (1). Antibradykinin activity of the nondialysate of the pulp has been examined here to obtain pharmacological evidence for its anti-inflammatory action (2). In this report, the results of partial purification of material having antibradykinin activity from A. saponaria on isolated guinea pig ileum and its proteolytic property against bradykinin are presented.

EXPERIMENTAL

Materials —The following materials were purchased from suppliers: dextran gel², hydrophilic polyvinyl gel², dialysis membrane³, synthetic bradykinin⁴, and bromelain⁷. The gel filtrations were performed at room temperature at a flow rate of 21 ml/hr using a microtube pump⁸.

Methods of Analysis—Protein and carbohydrate contents in samples

NOTES

REFERENCES

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