THE BIOAVAILABILITY OF ULTRAMICROSIZE GRISEOFULVIN (GRIS-PEG®) TABLETS IN MAN

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ABSTRACT

In an effort to provide for a better absorption and a more predictable blood level of griseofulvin, the drug was incorporated into a PEG-6000 formulation. This ultramicrosize formulation (called Gris-PEG® tablets) was compared to commercially available microsize griseofulvin in normal male volunteers. The two studies reported were a double-blind, single-dose, parallel-group design and a crossover design. The results derived from these two studies indicate that the oral absorption of griseofulvin, in man, is significantly enhanced by the PEG formulation since essentially the same plasma levels were achieved with 250 mg. of the ultramicrosize griseofulvin (Gris-PEG®) as were achieved with a 500-mg. dose of the marketed microsize form of griseofulvin. The bioavailability of 250 mg. of the ultramicrosize griseofulvin was equivalent to that of a 500-mg. dose of the microsize formulation.

INTRODUCTION

There is evidence that griseofulvin is poorly and irregularly absorbed in humans and it is possible that in many infections unresponsiveness to griseofulvin therapy may be due to poor absorption of the drug.

Blood-level studies carried out in several laboratories have shown that it is possible to improve intestinal absorption of griseofulvin by reducing its particle size. Plasma levels equal to those resulting from a full dose of macrosize griseofulvin (10 microns plus in diameter) can be obtained with one half the dose of microsize griseofulvin (2.7 micron plus in diameter).

The reduction of particle size can be accomplished directly by several
recognized techniques. The resultant fine particles may not produce the expected faster dissolution rate and better gastrointestinal absorption due to possible aggregation and agglomeration of the fine particles. This may be caused by the electrostatic charge that develops on the solids after milling.

The application of solid dispersion systems to increase rates of dissolution and oral absorption of poorly water-soluble or insoluble drugs was proposed by Sekiguchi and Obi in 1961. These authors described the formation of an eutectic mixture which consisted of a physiologically inert, readily soluble carrier plus a poorly water-soluble drug. A mixture of the drug and the carrier was melted together and then solidified by chilling or cooling to room temperature. At room temperature, this material was a solid material. When such a solid dispersion system was exposed to water or gastrointestinal fluids, the soluble carrier was rapidly dissolved, releasing finely dispersed particles of the drug. This was based upon the assumption that at the time of the solidification, only very small particles in the submicron or micron range would be formed. Chiou and Riegelman have described the in-vitro characteristics of solid dispersion of griseofulvin.

The in vivo applications with griseofulvin were only recently demonstrated by Chiou and Riegelman in dogs and human subjects. These investigators demonstrated that oral administration of griseofulvin in the solid dispersion formulations gave fast and almost complete absorption, whereas only 30 to 60 percent of the commercially available microsize formulation was absorbed. In their studies, they used polyethylene glycol (PEG-6000) as the dispersion carrier.

The human bioavailability studies reported in this paper were designed to corroborate and amplify the results presented by Chiou and Riegelman and to compare quantitatively the oral absorption characteristics of commercially available microsize griseofulvin tablets and ultramicrosize griseofulvin (Gris-PEG®) tablets (griseofulvin in a PEG-6000 formulation).

A group of thirty-six male volunteers participated in Study No. 1 which was a double-blind parallel-group design.

In the second study, Study No. 1A, a group of eleven male subjects participated in a double-blind crossover study.

METHODS

1. Study No. 1

In this first bioavailability study, thirty-six male volunteers were randomly assigned to one of three groups of equal size by means of a table of random numbers.
Group A (12 subjects) received a single oral dose of 500 mg. of a commercially available formulation (tablet) of microsize griseofulvin.* Group B (12 subjects) received two 125 mg. ultramicrosize griseofulvin** tablets (griseofulvin in a PEG-6000 formulation). Group C (12 subjects) received four 125 mg. ultramicrosize griseofulvin tablets. All subjects received the study medications at 8:00 a.m. with 4 to 6 ounces of water. Blood samples for the determination of the concentration of griseofulvin in plasma were obtained at zero time and at 0.5, 1, 2, 4, 6, 8, 10, 12, and 24 hours after the oral administration of the study medication.

2. Study No. 1A

Twelve normal healthy male volunteers were selected to participate in this double-blind, single-dose crossover study. Eleven subjects actually took part in this study. One subject never returned after the initial physical examination. Group I received a single oral dose of 500 mg. of a commercially available microsize formulation (tablet) with 4 to 6 ounces of water on Study Day 1. Group II received a single oral dose of 250 mg. of ultramicrosize griseofulvin with 4 to 6 ounces of water on Study Day 1. Assignment of subjects to a treatment group was based on a table of random numbers. On Study Day 9, following a washout period, which extended from Study Day 3 to Study Day 8, the subjects were crossed over and received the second study medication.

Blood samples for the determination of the concentration of griseofulvin in the plasma were obtained at zero time and at 0.5, 1, 2, 4, 6, 8, 10, 12, 24, 36, 48, and 72 hours after the oral administration of the study medications.

The following variables were controlled in both Study No. 1 and Study No. 1A. In both studies, all subjects were informed about the purpose and design of the experiment. All gave written consent to participate in these studies. Subjects selected indicated a willingness and good motivation to cooperate.

All subjects were between the ages of 21 and 50 years, weighed between 140 and 200 pounds and were within ±15 percent of the normal body weight for their frame and stature. Additional criteria for entrance into the studies included a normal routine physical examination, complete blood count, urinalysis and automated serum chemistries. Further, all subjects were totally free of significant clinical illness in the two weeks preceding the study; had no surgical or medical condition which might interfere with the absorption, metabolism or excretion of the study medications; were not taking any other medication.

During the pretreatment phase (control period), the following parameters were studied in each subject: a 12-lead ECG, a battery of hematology tests, including a determination of the hemoglobin, hematocrit and WBC count. Blood chemistries included a determination of the following: calcium, inorganic phosphorus, fasting blood sugar, BUN, serum uric acid, total protein, albumin, cholesterol, total bilirubin, alkaline phosphatase, LDH and SGOT.

Subjects with abnormal values or findings were not admitted into these studies. These parameters were evaluated again on Study Day 2 in Study No. 1. They were also evaluated again in Study No. 1A on Study Day 2, at the end of the washout period which was Study Day 8 and on Study Day 10.

No concurrent medication was permitted during the course of either Study No. 1 or No. 1A.

Each subject entered the Clinical Unit of the Baltimore City Hospital the night before the study was initiated and subjects fasted overnight but were

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* Microsize griseofulvin tablets were purchased from available commercial supplies.
** Ultramicrosize griseofulvin tablets were supplied by Sandoz, Inc.
allowed water *ad lib.* No food or liquids were allowed until four hours after the ingestion of the study medications.

The plasma samples were labeled with a five-digit number, frozen and kept frozen until the time of the assay. Schwarz *et al.*\(^2\) have recently reported upon the chemical assay method employed in the present studies.

The persons who performed the chemical assays were not aware of the study medications received by any subject.

In Study No. 1, the statistical procedures used were the analysis of variance, the t-test against zero time and the Krushal-Wallis rank sum test.

For Study No. 1A, the data from the plasma samples were statistically analyzed using the analysis of variance for a crossover design. Vital signs and clinical laboratory data were analyzed by comparing the change from baseline for the two treatments.

**RESULTS**

After the plasma assay results had been obtained, the following parameters were subjected to a statistical analysis:

a. peak plasma level;

b. time to reach peak plasma level;

c. area under the plasma level curve.

**Study No. 1 — Parallel-Group Design**

A single oral dose of 250 mg. of ultramicrosize griseofulvin produced essentially the same peak plasma concentration, the same time to

**Figure 1** — Study No. 1, the plasma concentration of griseofulvin (mcg./ml.) after a single oral dose in human volunteers; gas chromatographic assay.

- ○ = microsize griseofulvin 500 mg.
- ■ = ultramicrosize griseofulvin 250 mg.
- ▲ = ultramicrosize griseofulvin 500 mg.
reach peak concentration and the same area under the plasma level curve as was achieved with a single oral dose of 500 mg. of the microsize formulation of griseofulvin (Fig. 1). There was no statistically significant difference between the plasma levels achieved with these two study medications.

Following the oral administration of a single 500-mg. dose of ultramicrosize griseofulvin to man, the peak plasma level and the area under the plasma level curve were significantly enhanced when compared to the results obtained with a 500-mg. dose of a commercially available microsize formulation of griseofulvin (Fig. 1).

Study No. 1A — Crossover Design

In this crossover study, an oral dose of 250 mg. of ultramicrosize griseofulvin produced essentially the same peak concentration, the same time to reach peak concentration, and the same area under the plasma level curve as was achieved with a single oral dose of 500 mg. of a commercially available microsize formulation of griseofulvin. The differences between the two study medications were not significant (Fig. 2).

Figure 2 — Study No. 1A, the plasma concentration of griseofulvin (mcg./ml.) after a single oral dose in human volunteers; gas chromatographic assay.
The numerical values for the bioavailability parameters studied in Studies No. 1 and No. 1A have been summarized in Table I.

Table I — Bioavailability Parameters — Average Values

<table>
<thead>
<tr>
<th>Study No.</th>
<th>N</th>
<th>Group</th>
<th>Oral Dose-mg.</th>
<th>Time To Peak (Hr.)</th>
<th>Peak Plasma Level (mcg./ml.)</th>
<th>Area Under Plasma Level Curve (Hrs. mcg./ml.)</th>
</tr>
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<tbody>
<tr>
<td>No. 1</td>
<td>12</td>
<td>A</td>
<td>500</td>
<td>4.00</td>
<td>0.65</td>
<td>9.89</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>B</td>
<td>250</td>
<td>4.67</td>
<td>0.80</td>
<td>11.18</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>C</td>
<td>500</td>
<td>4.17</td>
<td>1.15</td>
<td>15.11</td>
</tr>
<tr>
<td>No. 1A</td>
<td>11</td>
<td>I</td>
<td>500</td>
<td>6.10</td>
<td>0.51</td>
<td>14.36</td>
</tr>
<tr>
<td></td>
<td>11</td>
<td>II</td>
<td>250</td>
<td>3.70</td>
<td>0.60</td>
<td>12.88</td>
</tr>
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</table>

A = Microsize Griseofulvin — 500 mg.
B = Ultramicrosize Griseofulvin — 250 mg.
C = Ultramicrosize griseofulvin — 500 mg.
I = Microsize Griseofulvin — 500 mg.
II = Ultramicrosize Griseofulvin — 250 mg.

In studies No. 1 and No. 1A, no adverse effects attributable to the study medications were observed in the following parameters: vital signs, ECG, hematology parameters, blood chemistry parameters and the urinalysis tests. No adverse reactions were reported during the course of these two studies.

Table II — Study No. 1 — Summary of Background Data
Mean ± Standard Deviation

<table>
<thead>
<tr>
<th>Drug Group</th>
<th>Age In Years</th>
<th>Weight In Lbs. (Kg.)</th>
<th>Height In Inches (Cm.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>24.1 ± 2.4</td>
<td>160.3 ± 15.8</td>
<td>69.4 ± 2.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(72.71 ± 7.1 kg.)</td>
<td>(176.2 ± 6.1 cm.)</td>
</tr>
<tr>
<td>B</td>
<td>27.2 ± 5.3</td>
<td>160.4 ± 16.4</td>
<td>69.1 ± 3.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(72.76 ± 7.4 kg.)</td>
<td>(175.5 ± 8.8 cm.)</td>
</tr>
<tr>
<td>C</td>
<td>24.1 ± 2.0</td>
<td>156.5 ± 15.9</td>
<td>70.4 ± 2.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(70.99 ± 7.2 kg.)</td>
<td>(178.8 ± 5.1 cm.)</td>
</tr>
</tbody>
</table>

A = Microsize Griseofulvin — 500 mg.
B = Ultramicrosize Griseofulvin — 250 mg.
C = Ultramicrosize Griseofulvin — 500 mg.

For both Studies No. 1 and No. 1A, there were no significant differences between treatment groups in terms of age, body weight and height as indicated in Tables II and III.
Table III — Study No. 1A — Summary of Background Data

Mean ± Standard Deviation — Study Day 0

<table>
<thead>
<tr>
<th>N</th>
<th>Drug Group</th>
<th>Age in Years</th>
<th>Weight in Lbs. (Kg.)</th>
<th>Height in Inches (Cm.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>I</td>
<td>25.6 ± 3.5</td>
<td>150.0 ± 9.2</td>
<td>70.2 ± 1.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(68.95 ± 4.2 kg.)</td>
<td>(178.3 ± 4.8 cm.)</td>
</tr>
<tr>
<td>6</td>
<td>II</td>
<td>22.3 ± 1.0</td>
<td>157.6 ± 5.1</td>
<td>70.7 ± 2.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(71.49 ± 2.3 kg.)</td>
<td>(179.5 ± 6.8 cm.)</td>
</tr>
</tbody>
</table>

I = Microsize Griseofulvin — 500 mg.
II = Ultramicrosize Griseofulvin — 250 mg.

DISCUSSION

The results derived from these two studies confirm those of Chiou and Riegelman\(^1\) and indicate that the oral absorption of griseofulvin in man is significantly enhanced by the PEG formulation since essentially the same plasma levels were achieved with 250 mg. of ultramicrosize griseofulvin as were achieved with a 500-mg. oral dose of a marketed microsize formulation of griseofulvin.

The parameters peak plasma level and area under the plasma level curve produced by an oral dose of 500 mg. of the ultramicrosize griseofulvin were 1.48 times as large as those obtained with a 500-mg. dose of the microsize griseofulvin (Fig. 1), \(P = < 0.01\).

The results obtained from these studies conducted in man indicate that the PEG formulation significantly enhanced the oral absorption of griseofulvin and should provide for a better absorption and for a more predictable blood concentration.

Analysis of the data obtained from the two studies reported upon in this paper indicate that the bioavailability of 250 mg. of ultramicrosize griseofulvin (griseofulvin in a PEG-6000 formulation) was equivalent to the bioavailability of a 500-mg. dose of a commercially available microsize formulation of griseofulvin, within the limits of the pharmaceutical tolerance.

The increased absorption is thought to be due to the ultramicrosize particles of griseofulvin obtained with the PEG-6000 formulation.

Acknowledgements

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The statistical analysis was done under the supervision of Hans
Mueller, Ph.D., Director, Department of Research Data Services, Sandoz, Inc., East Hanover, New Jersey.

References:


