EFFECT OF FOOD ON THE BIOAVAILABILITY OF GRISEOFULVIN FROM MICROSIZE AND PEG ULTRAMICROSIZE (GRIS-PEGR) PLAIN TABLETS

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Effect of food on the bioavailability of griseofulvin from its two plain tablets, a commercial microsize product and a PEG ultramicrsize (GRIS-PEGR) one, was investigated. The drug was dissolved at a slower rate from ultramicrsize formulation than from microsize one in 18 l of pH 7.2 buffer but at a little faster rate in 40% dimethylformamide. When administered to fasting subjects, the microsize product showed higher serum levels and peak serum level than ultramicrsize one but the extent of the bioavailability was nearly the same. A standard breakfast enhanced the rate of absorption of the drug from both the products, especially from ultramicrsize one, and those products were equivalent in the rate and extent of bioavailability after food ingestion. The peak serum level of ultramicrsize product in nonfasting was about twice higher than that in fasting subjects. The different intensities of food effect on the bioavailabilities from two dosage forms suggest that formulation factors should be considered for the evaluation of food effect.

Keywords—griseofulvin; ultramicrsize formulation; microsize formulation; dissolution; food effect; human study; bioavailability

INTRODUCTION

Bioavailabilities of drug have been usually estimated in a fasting state to avoid the complicated interference with food. However, it seems important to investigate the availability after food ingestion because drugs are often or mostly administered after food intake, and alteration of the bioavailability due to food, if occurs, may cause a significant change in the clinical response. There is a considerable evidence to indicate that the absorption of drugs may be influenced by the presence of food in the gastrointestinal tract but most of the investigations have been carried out with only one formulation but not with different ones without any detail information on the formulation characteristics. However, food effect on drug bioavailabilities from its dosage forms may differ by the lots and type of the formulations as shown in nitrofurantoin and erythromycin formulations. In our previous studies on chloramphenicol, food enhanced the bioavailability from sugar coated tablet which had poor availability in fasting state but it did not from the powder. Thus it should be necessary to consider the formulation characteristics and pay attention as to whether the food effect, if was observed, is mainly based on the interactions of food with drug itself or with formulation factors.

Considerable interest has been generated concerning the absorption of griseofulvin because of the low water solubility and hence its poor bioavailability. The absorption of griseofulvin was increased by fatty meals probably because of enhancement of the solubility and decreased gastric emptying rate. The present investigation was undertaken to study how food ingestion influences the bioavailability of griseofulvin from its two different plain tablets, a commercial microsize product and a PEG ultramicrsize (GRIS-PEGR) one.

METHODS

Formulations—PEG ultramicrsize griseo-
fulvin tablet (GRIS-PEG®) (Dorsey Laboratories, Division of Sandoz Inc.) which is formulated with the drug dispersed in polyethylene glycol 6000 and a commercial plain tablet of microsize griseofulvin in Japan were used in this study. The labellings of both products indicate that each tablet contains 125 mg of griseofulvin. The spectrophotometric assay showed that the contents of the drug in a tablet of the ultramicrosize and microsize products were 123 and 122 mg, respectively.

Disintegration Time—Disintegration times of the tablets were determined with six tablets according to JP-IX specifications using pH 1.2 hydrochloric acid solution and pH 7.2 sodium phosphate buffer (0.01 M).

Dissolution Rate—The dissolution rates of the drug from its dosage forms were determined with one tablet at 37°C in 18 l of pH 7.2 sodium phosphate buffer (0.01 M) and in 900 ml of 40% (w/v) dimethylformamide. Eighteen liters of pH 7.2 buffer was agitated with three bladed screw type impeller (5.0 cm i.d.) at 512 rpm in the middle of the solvent in a 20 l flat-bottom beaker (29.0 cm i.d.). Dissolution test in 900 ml of 40% dimethylformamide was carried out by paddle method (USP XX) at 120 rpm. The amount of the drug dissolved was monitored spectrophotometrically by passing the solution through a glass filter (porosity G-3) to a flow cell. An average dissolution rate was obtained after three dissolution runs.

Bioavailability—Four healthy male subjects participated in this four way cross-over study ranged in age from 32 to 51 years (mean 43), in height from 160 to 172 cm (mean 168) and in weight from 54 to 68 kg (mean 60). Each subject received a test tablet with 200 ml of water after fasted overnight or 15 minutes after ingestion of a standard breakfast which consists of 100 g of bread, 20 g of butter, 35 g of cucumber, 200 ml of milk and a boiled egg. No foods or liquid were permitted until 4 h after drug administration. Blood samples (5 ml) were obtained at 1, 3, 5, 8, 23.5, 33 and 47.5 h after dosing and serum samples were stored frozen at −15°C until assayed.

The experiments were repeated every two weeks. Serum griseofulvin was determined by gas-chromatography. The differences among the treatments in serum levels, peak serum levels (Cmax), time to Cmax (Tmax), area under serum concentration-time curves from zero to 47.5 h and to infinite time (AUC47.5 and AUC∞), elimination rate constants (k(el) and half lives (t1/2) were examined statistically by analysis of variance (ANOVA) and then by Tukey's multiple range test. The Cmax and Tmax were observed values and k(el) or t1/2 was calculated from the serum concentration-time curve from 23.5 to 47.5 h. AUC47.5 and AUC∞ were calculated by the trapezoidal rule and the method of Wagner, respectively.

RESULTS

The dissolution rates of griseofulvin from its

FIG. 1. Dissolution of Griseofulvin from Microsize (O) and Ultramicrosize (●) Formulations in 18 l of pH 7.2 Phosphate Buffer

The solid and dotted lines show the dissolution curves in the absence of surfactants and in the presence of 0.1%(w/v) polysorbate 80.
dosage forms were determined in 18 l of aqueous solvent as Katchen et al. had applied and in 900 ml of 40% dimethylformamide since the drug is practically insoluble in water and the use of partially alcoholic medium was described for the dissolution tests of poorly soluble drugs in USP Pharmacopeial Forum. As Fig. 1 shows, the drug was dissolved slower from the ultramicrosize product than from microsize one, and polysorbate 80 did not influence the dissolution though the surfactant was expected to promote the dissolution of the drug due to its wetting action. As Fig. 2 shows, in 40% dimethylformamide solution the ultramicrosize formulation showed faster dissolution than microsize one contrary to the dissolution findings in pure aqueous medium. This indicates that the high solvent capacity of dimethylformamide having lipophilic and hydrophilic properties will change the dissolution behavior of griseofulvin from its dosage forms.

The disintegration time of the ultramicrosize product was as fast as that of microsize one at pH 7.2 and was a little faster at pH 1.2 (Table I). The microsize product disintegrated into fine particles while the ultramicrosize one produced relatively large particles and/or agglomerates after disintegration at either pH 7.2 or 1.2, which may be related with slower dissolution from ultramicrosize product in aqueous solvent.

Fig. 3 shows the mean serum concentration of griseofulvin after oral administration of two formulations to fasting and nonfasting subjects, and Table II lists the mean values of the in vivo parameters. When administered to fasting subjects, the microsize product exhibited higher

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Solvent pH 7.2</th>
<th>Solvent pH 1.2</th>
</tr>
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<tbody>
<tr>
<td>Microsize</td>
<td>12.0±1.1</td>
<td>10.8±0.7</td>
</tr>
<tr>
<td>Ultramicrosize</td>
<td>11.8±2.7</td>
<td>7.3±1.8</td>
</tr>
</tbody>
</table>

The figures show means ± standard deviations of the disintegration times determined with six tablets.

![Graph showing dissolution of griseofulvin](image)

**FIG. 2.** Dissolution of Griseofulvin from Microsize (○) and Ultramicrosize (●) Formulations in 900 ml of 40% Dimethylformamide

**TABLE I.** Disintegration Times (Min) of Microsize and Ultramicrosize Griseofulvin Tablets

**FIG. 3.** Mean Serum Concentrations of Griseofulvin after Oral Administration of Microsize and Ultramicrosize Formulations to Fasting and Nonfasting Human Subjects

Ultramicrosize formulation (●) and microsize formulation (○). The dotted and solid lines show the serum levels in fasting and nonfasting states respectively. The vertical lines show standard errors.
Bioavailability of Griseofulvin

serum levels from zero to 8 h after dosing and $C_{\text{max}}$ than ultramicrosize one. The $C_{\text{max}}$ of ultramicrosize product was approximately 70% of microsize's one and the difference was statistically significant. No significant difference was observed between the AUC_s of both tablets given in fasting state.

The standard breakfast significantly enhanced the serum levels at 3 and 5 h and $C_{\text{max}}$ of microsize formulation. The $C_{\text{max}}$ in nonfasting was approximately 136% that in fasting. The standard breakfast increased more the serum levels at earlier sampling times and $C_{\text{max}}$ of ultramicrosize formulation, and the $C_{\text{max}}$ was about twice that in fasting. Under food ingestion condition, the bioavailability of ultramicrosize formulation was nearly equal to that of microsize one. The food, however, did not significantly influence the AUC_s and $T_{\text{max}}$ of both formulations though the $T_{\text{max}}$s in nonfasting, especially that of ultramicrosize one, tended to decrease in comparison with that in fasting.

The elimination half lives of griseofulvin were 11 - 13 h which agreed with that reported by Rowland et al. Food ingestion did not affect the elimination rate of the drug.

DISCUSSION

The dissolution and hence absorption of griseofulvin has been reported to be enhanced by reducing particle size of the crystals. Thus a microsize powder of the drug is used in commercial tablets and a new formulation called ultramicrosize griseofulvin tablet can also be obtained, which was shown to have twice better bioavailability than that of microsize one. However, Straughn et al. recently found lower absorption of the drug from ultramicrosize formulations than from microsize ones. In this study, the drug was absorbed at a slower rate from ultramicrosize product than from microsize one in fasting subjects, which coincided with the result of Straughn et al.

A standard breakfast increased the serum levels in absorption phase and $C_{\text{max}}$ of both formulations. The food, especially the fat in it, seems to directly facilitate the dissolution of griseofulvin and also increase it indirectly by stimulating the flow of bile containing solubilizing and emulsifying agents. The breakfast greatly

| TABLE II. Serum Concentrations, $C_{\text{max}}$, $T_{\text{max}}$, AUC and Elimination Rates after Oral Administration of Microsize and Ultramicrosize Griseofulvin Tablets to Fasting and Nonfasting Subjects |
|-----------------|----------------|----------------|----------------|
| In vivo parameter | Ultramicrosize product | Microsize product | Results of ANOVA |
|                  | Fasting (a) | Nonfasting (A) | Fasting (b) | Nonfasting (B) | Tukey's test b) |
| 1.0h             | 0.131 ± 0.015 | 0.343 ± 0.121 | 0.219 ± 0.053 | 0.478 ± 0.168 | N.S a) |
| 3.0              | 0.264 ± 0.049 | 0.684 ± 0.035 | 0.479 ± 0.050 | 0.671 ± 0.048 | p < 0.01 A>B >b >a |
| 5.0              | 0.318 ± 0.067 | 0.601 ± 0.067 | 0.460 ± 0.029 | 0.671 ± 0.035 | p < 0.01 A>B >b >a |
| 8.0              | 0.235 ± 0.042 | 0.480 ± 0.046 | 0.400 ± 0.044 | 0.470 ± 0.060 | N.S |
| 23.5             | 0.252 ± 0.027 | 0.190 ± 0.031 | 0.227 ± 0.030 | 0.174 ± 0.026 | N.S |
| 33.0             | 0.159 ± 0.031 | 0.113 ± 0.025 | 0.130 ± 0.023 | 0.110 ± 0.024 | N.S |
| 47.5             | 0.082 ± 0.024 | 0.046 ± 0.009 | 0.056 ± 0.010 | 0.051 ± 0.016 | N.S |
| $C_{\text{max}}$(µg/ml) | 0.359 ± 0.036 | 0.684 ± 0.035 | 0.517 ± 0.032 | 0.703 ± 0.041 | p < 0.01 A>B >b >a |
| $T_{\text{max}}$(h) | 9.4 ± 4.7 | 3.0 ± 0.0 | 4.3 ± 1.3 | 3.0 ± 1.2 | N.S |
| AUC_{0-8} (µg.h/ml) | 9.34 ± 0.70 | 11.89 ± 1.2 | 10.93 ± 1.04 | 11.95 ± 1.40 | N.S |
| AUC_{inf} (µg.h/ml) | 10.77 ± 1.14 | 12.67 ± 1.37 | 11.90 ± 1.25 | 13.06 ± 1.87 | N.S |
| $k_{el}$(h^{-1}) | 0.057 ± 0.004 | 0.060 ± 0.003 | 0.059 ± 0.002 | 0.057 ± 0.008 | N.S |
| $t_{1/2}$(h) | 12.3 ± 0.7 | 11.6 ± 0.6 | 11.8 ± 0.5 | 13.0 ± 1.9 | N.S |

The figures indicate means ± standard errors. a) N.S: not significant. b) Treatments underlined by a common line did not differ significantly.
increased the absorption rate of the drug from ultramicrosize formulation and it was nearly equal to that from microsize one in the presence of food though lower in the absence of it. Ultramicrosize formulation may produce relatively large particles or agglomerates by disintegration in fasting state as shown in the in vitro disintegration test, but further disintegration and deaggregation of those particles may be accelerated by food ingestion. Previous studies on chloramphenicol suggested the strong destructive force caused by food. 3) On the other hand, the fat component in the diet may make the difference smaller in the dissolution rates of lipophilic drugs such as griseofulvin from different formulations, together with enhancement of the dissolution, as shown in nitrofurantoin studies 2) in which the macrocrystalline drug was absorbed at a slower rate than microcrystalline one in fasting state but absorbed at the same rate in non-fasting state. The in vitro dissolution behaviors of griseofulvin in 40% dimethylformamide may suggest the dissolution in a lipophilic state.

$T_{\text{max}}$, especially of ultramicrosize formulation, tended to be decreased by ingestion of the breakfast. It will be the net result of counteracting effects of food on the absorption of the drug, namely the retardation of gastric emptying rate 4) and enhancement of the disintegration and dissolution of the drug.

The different intensities of food effect on the bioavailabilities from microsize and ultramicrosize formulations suggest that its effect on the absorption of the other drugs may also differ by the lots and type of the formulations, and it seems necessary to pay attention whether the observed effect of food will be attributed to the interaction between food and drug itself, or that between food and formulation factors.

REFERENCES