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THE BIOAVAILABILITY OF GRISEOFULVIN FROM MICROSIZED AND ULTRAMICROSIZED TABLETS IN NONFASTING VOLUNTEERS

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Abstract : Tablets of either microsized or ultramicrosized griseofulvin (2×125mg), were administered to 6 healthy volunteers of either sex just before a breakfast containing 4o g. of butter. The plasma concentration of griseofulvin were determined 1, 3, 5, 7, 9, 24, and 32 h. after dosing using a spectrofluorometric method, and pharmacokinetic parameters (Cp max, t max, AUC 0 −> 32) were calculated.

These parameters were found to be; Cp max = 0.0.681 ± 0.1 μ/ml, t max = 2.51 ± 0.33 h. and AUC = 14.14 ± 2.33 μg h/ml for microsized tablets and Cp max = 0.80 ± 0.08 ±g/ml, t max = 2.44 ± 0.54 and AUC = 16.25 ± 1.16 μg h/ml for ultramicrosized tablets.

Our results show that mean peak plasma level and AUC (0 −> 32) are only slightly higher for the ultramicrosized preparation and the time to peak plasma level is similar in two preparations. Therefore, it is concluded that coadministration of griseofulvin with food will tend to reduce the difference between the bioavailability of the two type of preparations.

Key words : griseofulvin bioavailability nonfasting volunteers microsized & ultramicrosized tablets

INTRODUCTION

Griseofulvin an orally administered antifungal agent, is used in the treatment of mycotic diseases of the skin, hair and nails. Because of its poor water solubility, oral administration of this drug may be subject to variable and incomplete absorption. In order to improve oral absorption tablets and capsules are formulated to contain microsize crystals of griseofulvin. Erratic and incomplete absorption with these formulations is still possible as shown by the sensitivity of griseofulvin bioavailability to the dissolution rate of the tablets (1, 2). Recently products have been formulated with the drug dispersed in polyethylene glycol 6000 (3, 4). The labeling of these commercially available "Ultramicorsize" formulations indicates that the efficiency of absorption from the ultramicrocrystalline griseofulvin is approximately twice that of the conventional microsize griseofulvin (5, 6) permitting oral administration of half as much griseofulvin per tablet. Since griseofulvin tablets is usually administered with food and the absorption of this drug from the gastrointestinal tract is substantially increased by coadministration with a fatty meal (7), the present work was carried out to investigate the effect of food upon the bioavailability of the drug from microsize and ultramicrosize tablets.

METHODS

Formulation : One commercial microsize griseofulvin tablet available in Iran (Daru Pakhsh Co.) and one ultramicrosize griseofulvin tablet (Wander Co. Switzerland) were used.

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Bioavailabilability : Griseofulvin were administered to 6 healthy volunteers (one female and five males; age, 26 to 31 yrs; weight, 33 to 61 kg.) just before a breakfast containing 40g to butter. Before the study the participants were given a clinical examination to ensure they were healthy. All of the subjects were prohibited from taking medicines and alcoholic beverages from 7 days before the drug administration to the end of the test. Each subject took two tablet orally with 200 ml of water and then breakfast was served. Blood samples (10ml) were obtained at 1, 3, 5, 7, 9, 24, and 32 h. after drug administration and the plasma samples were kept frozen at 15° C until assayed. Model independent pharmacokinetics parameters [Cp max, t max, AUC (0 −> 32)] were calculated from the Plasma concentration of griseofuvlin at various times. The study was repeated after *15* days using the same volunteers, who now consumed the other type of tablets than those used in previous study.

Assay : The plasma griseofulvin concentration was determined by a spectrofluorometric method described previously (8). The method was modified slightly; to 1.0 ml of plasma in a stoppered test tube was added 10 ml of ethanol 1% followed by 10 ml of anhydrous ether. The test tube was shaken for 1 min. A 9 ml aliquot of the ether layer was transferred to a 10 ml test tube and evaporated to dryness with nitrogen. The residue was dissolved in 2.5 ml of 80% methanol (V/V) and shake for 20 min. The fluorescence was read in a spectrofluorometer (Perkin Elmer) with the following settings : excitation wavelength, 300 nm; detection wave length, 420 nm.

RESULTS

Figures 1 and 2 show the serum concentration-time curves of griseofulvin in healthy volunteers after oral administration of microsize and ultramicrosize preparations respectively. The bioavailability of griseofulvin from ultramicrosize tablets is more uniform than that of microsize tablets as indicated by less intraindividual variations. The pharmacokinetics parameters (Table I) show that the mean time to peak plasma level for ultramicrosize and microsize tablets are comparable. However the maximum plasma level and AUC (0 −> 32) μg h/ml are slightly higher for ultramicrosize preparations. The plasma half life of griseofulvin is smaller for the ultramicrosize preparations.

TABLE I: Pharmacokintic parameters for griseofulvin after administration of either microsized or ultra-microsized tablets in non-fasting volunteers.

Parameter	*Unit*	*Microsized tablets mean±SEM*	*Ultra-microsized tablets mean±SEM*	*t-test*
t 1/2	hr	20.88±2.55	13.90±2.03	p<0.1
AUC 0−>32	μg h/ml	14.14±2.33	16.25±1.16	N.S.
t max	hr	2.515±0.33	2.440±0.54	N.S.
Cp max	μg/ml	.6815±0.10	.8043±0.079	N.S.

DISCUSSION

The bioavbailability of griseofulvin (as indicated from its AUC) after its administration to fasting volunteers, is reported to be much higher for ultramicrosize tablets compared to microsized tablets (9, 10). Similarly, ultramicrosize tablets produce much higher peak plasma level (0. 79-0.86 μg/ml, compared to 0.52-0.58 μg/ml for microsized tablets) and peak level will be reached much faster (3.3-3.8 hr compared to 9.1-9.2 hr for microsize preparations). In contrast to results in fasting volunteers, our results show that when griseofulvin was administered with a fatty meal in this study the difference between ultramicrosize and microsize preparations was not significant and both preparations are absorbed to the same extent and with same rates, comparable to those following administration of ultramicrosized tablet to fasting volunteers. Therefore it can be concluded that administration of griseofulvin preparations with a fatty meal will tend to reduce the differences between various preparations. This may have resulted from the dissolution of griseofulvin in lipids inside GI lumen. It has been previously shown that the bioabailability of griseofulvin is markedly enhanced by concomintent inagestion of food and milk (11).

However, the intraindividual variation is much

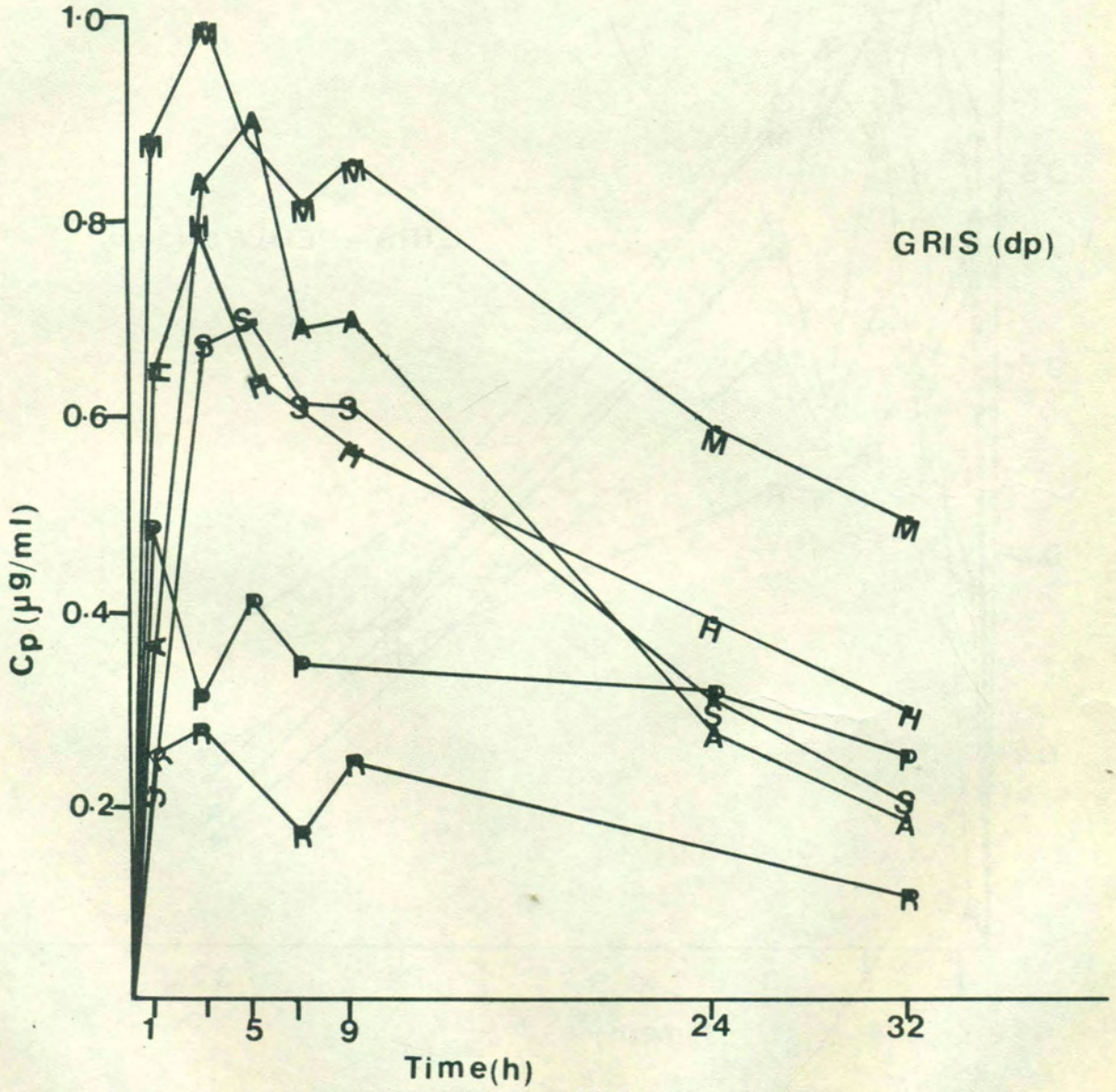

Fig. 1: Individual plasma concentration of griseofulvin after administration of two 125 mg microsized griseofulvin tablets (Gris dp) to 6 healthy and non-fasting volunteers. The letters refer to individual volunteers.

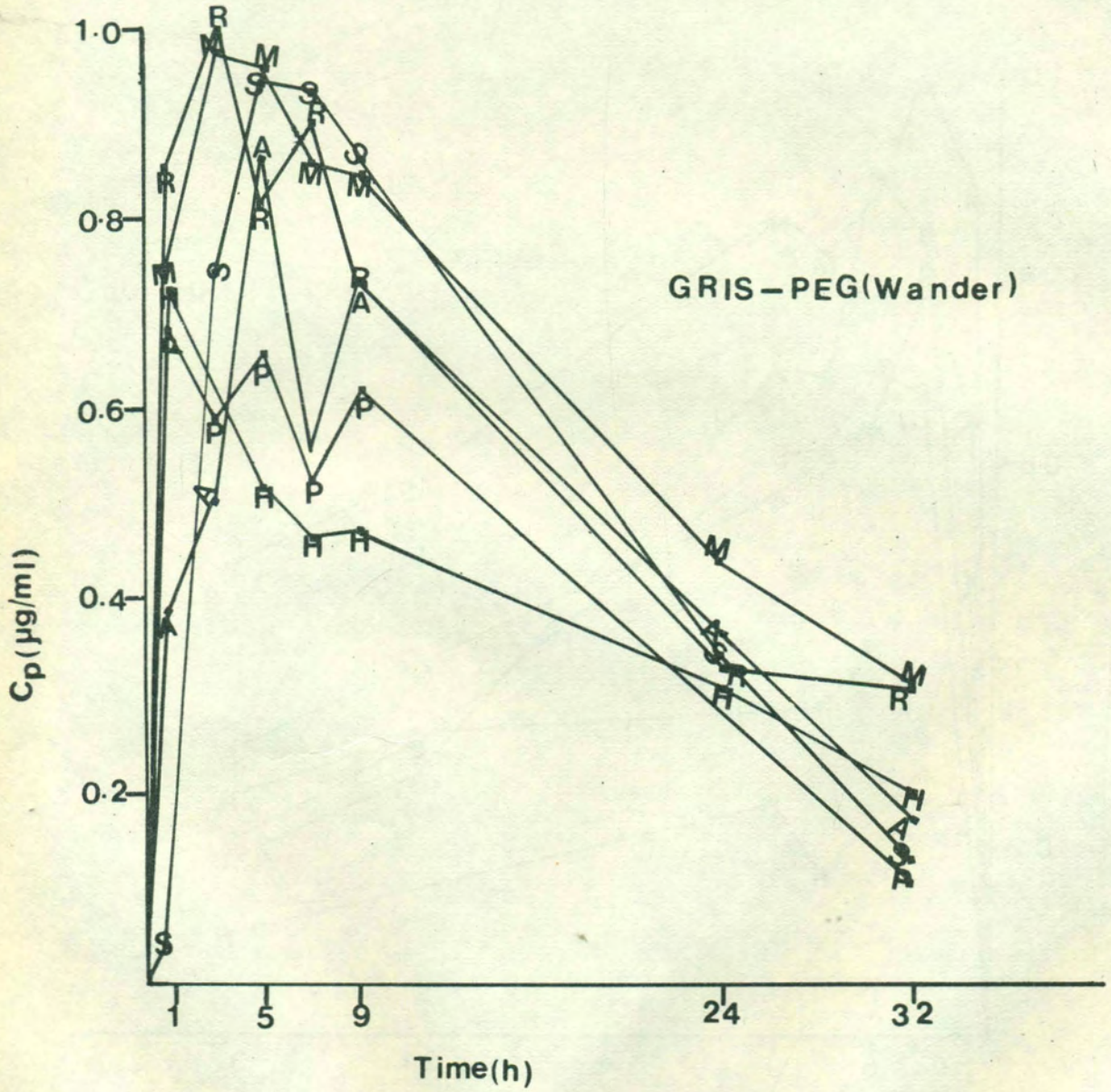

Fig. 2: Individual plasma concentration of griseofulvin after administration of two 125 mg ultra-microsized griseofulvin tablets (GRIS-PEG) to 6 healthy and non-fasting volunteers. The letters refer to same individual volunteers as in Fig. 1.

less for the ultramicrosize tablets and its apparent t 1/2 is lower compared to microsized tablets (Figs. 1 & 2 and table II). Since apperant t 1/2 of griseofulvin is dependent on its rate of absorption (9) the lower t 1/2 for ultramicrosized tablets is indicative of faster rate of absorption for this preparation.

In conclusion, this study shows that coadministration of griseofulvin with food tend to minimize the difference between various preparations, but the griseofulvin absorption from ultramicrosized tablets still is more reliable and uniform. Therefore, while ultramicrosized formulation does not justify a reduced dosage, is still preferable preparation.

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