suggests that incomplete absorption in β-blockers is associated with the observed non-pH-partition route of absorption.

REFERENCES

Collins, R. F., George, C. F. (1976) Br. J. Clin. Pharmacol. 3: 346P

Cruickshank, J. M. (1980) Am. Heart. J. 100: 160–178

Dolusio, J. T., Billups, N. F., Dittert, L. W., Sugita, E. T., Swintosky, J. V. (1969) J. Pharm. Sci. 58: 1196–1200

Dreyfuss, J., Brannick, J. L., Vukovich, R. A., Shaw, J. M., Willard, D. A. (1977) J. Clin. Pharmacol. 17: 300–305

Fourtillan, J. B., Lefebure, M. A., Courtois, P., Saux, M. C. (1981) Therapie 38: 457–463

George, C. F., Gruchy, B. S. (1979) J. Pharm. Pharmacol. 31: 643–644

Higuchi, W. I., Ho. N. F. H., Park, J. Y., Komiya, I. (1979) in: Prescott, L. F., Nimmo, W. S. (eds) 'Drug Absorption: Proceedings of the Edinburgh International Conference'. ADIS Press, 21 pp 35–60

Ho, N. F. H., Park, J. Y., Ni, P. F., Higuchi, W. I. (1983) in: Crouthamel, W., Sarapu, A. C. (eds) 'Animal Models for Oral Drug Delivery in Man'. APhA Academy of Pharmaceutical Sciences, Washington, USA, pp 27–107

Lucas, M. (1983) Gut 24: 734–739

McAinsh, J. (1977) Postgrad. Med. J. 53: 74–78

Reeves, P. (1979) Xenobiotica 9: 453–458

Schoenwald, R. D., Huang, H.-S. (1983) J. Pharm. Sci. 72: 1266

Taylor, D. C., Grundy, R., Loveday, B. (1981) Ibid. 70: 516–521

J. Pharm. Pharmacol. 1985, 37: 283–284
Communicated June 13, 1984

Fat contents of meals and bioavailability of griseofulvin in man

F. A. OGUNBONA†*, I. F. SMITH‡, O. S. OLAWOYE‡, †*Department of Pharmaceutical Chemistry, Faculty of Pharmacy and* ‡*Department of Community Health and Nutrition, Faculty of Health Sciences, University of Ife, Ile-Ife, Nigeria*

The bioavailability of griseofulvin was followed in twelve healthy volunteers by measuring the urinary excretion of the major metabolite 6-demethylgriseolfulvin, after each volunteer had ingested one 500 mg griseofulvin tablet under (1) fasting conditions, (2) immediately after a typical low-fat and (3) high-fat Nigerian meals. An increase of about 70 and 120% absorption occurred with the ingestion of the low-fat and high-fat meals respectively compared to the fasting state ($P < 0.01$). The maximum excretion rates of the free metabolite ($V_{max.}$) were also significantly increased ($P < 0.01$) following consumption of low and high fat meals. Our results thus suggest that the higher the fat content of the meals the higher the enhancement of the bioavailability of griseofulvin in man.

Griseofulvin is poorly soluble and a high fat diet has been listed among factors enhancing its absorption (Crounse 1963; Kabasakalian et al 1970; Khalafalla et al 1981). We have investigated the effect of Nigerian meals, composed of protein, carbohydrate and fat food sources on the bioavailability of griseofulvin in man as estimated from the cumulative urinary excretion of the major metabolite, 6-demethylgriseofulvin (6-DMG).

Materials and methods

The 6-DMG sample used for the preparation of calibration curve was isolated from the urine of a volunteer who had ingested one 500 mg griseofulvin tablet. The sample, purified and characterized had m.p. 286–288 °C (cf. 287 °C Arkley et al 1962). It gave a single spot (R_F 0·30) on a silica gel plate developed in chloroform–water–acetic acid (4 : 1 : 1) while griseofulvin had R_F of 0·90 on the same plate. The ^1H nmr of griseofulvin showed three methoxy groups at δ 3·63, 3·95 and 4·03 ppm ($CDCl_3$) whereas that of the 6-GMG sample showed only two methoxy groups at δ 3·65 and 3·83 ppm ($DMSOd_6$). The direct inlet mass spectrum of the sample gave M^+ at m/z 338 (36%) whereas that of griseofulvin gave M^+ at m/z 352 (42%). Sulphatase containing B-glucuronidase activity was obtained from Sigma Co., USA, 500 mg Grisovin tablets (Lot ILP 613) were kindly supplied by the Pharmacy Division of the University of Ife Health Centre.

The low-fat meal—corn gruel (pap) with fried bean balls (akara)—contained 29·3% fat calories while the high-fat meal, fried plantain with corned beef stew, contained 52·4% fat calories.

Twelve healthy male volunteers aged between 20–32 years (mean 24 ± 1) and 63 ± 2 kg (±s.e.m.) were instructed to abstain from taking any medicine or alcohol three days before the drug administration and throughout the trial. After fasting overnight each volunteer emptied his bladder just before taking the drug by mouth as one griseofulvin tablet (500 mg) with 200 ml of water. No liquid or food was allowed until 4 h after taking the tablet. The procedure was repeated a week later when the tablet was taken immediately after a low-fat meal, and after another week immediately after the high-fat meal. All volunteers received equal and identical meal portions. Total urine voided was collected at two-hourly intervals up to 12th hour and at the 24th hour after drug administration. The volume and pH of the urine samples were measured as soon as possible after collection. Samples were placed in well-stoppered tubes and stored at 5 °C until analysed for free 6-DMG according to Rowland & Riegelman (1973)

* Correspondence.

in duplicate. A calibration curve was plotted using urine spiked with 6 DMG (10–100 μg ml^{-1}).

Total 6-DMG was assayed by the same procedure after incubating overnight at 37 ± 0·5 °C a diluted urine sample (0·5 ml urine + 1 ml McIlavaine buffer, pH 6·8 + 3·5 ml water) with about 10 mg of the sulphatase powder containing β-glucuronidase activity. The data was analysed using analysis of variance (Snedecor & Cochran 1967). The differences between means were tested using Duncan's New Multiple Range Test (Steel & Torrie 1960).

Results and discussion

The 24 h cumulative urinary excretion of free and total 6-DMG after oral administration of 500 mg griseofulvin tablets to 12 volunteers is as illustrated in Fig. 1. These data were used to assess the bioavailability of griseofulvin since excretion data of the metabolite have been shown to be a direct measure of the absorption

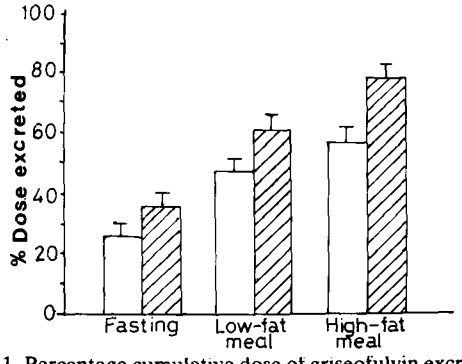

Fig. 1. Percentage cumulative dose of griseofulvin excreted as 6-demethylgriseofulvin (6-DMG) in 24 h following oral administration of 500 mg. Griseofulvin to 12 volunteers under three conditions. Open columns free 6-DMG. Hatched columns total 6-DMG (with s.e.m.).

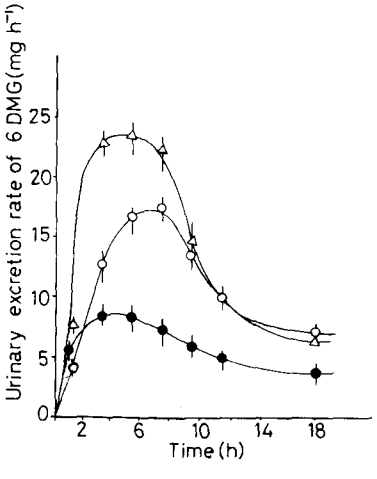

Fig. 2. Urinary excretion rate of free 6-demethylgriseofulvin following oral administration of 500 mg griseofulvin to 12 volunteers under three conditions. ● Fasting; ○ low-fat meal; △ high-fat meal.

characteristics of the drug (Kasabakalian et al 1970; Bates & Sequeira 1975). A general increase in the amount of griseofulvin absorbed was observed in all subjects as a result of the food intake before drug administration. The cumulative amounts of 6-DMG excreted under fasting conditions, and after the consumption of typical Nigerian low-fat and high-fat meals were 36·3 ± 3·5 (±s.e.m.) 61·5 ± 4·2 and 80·4 ± 5·4% of the dose administered, respectively. Thus, an increase of about 70 and 120% absorption appeared to have occurred with the consumption of the low-fat and high-fat meal respectively. These data showed significantly increased absorption of griseofulvin following both low and high meals compared with the fasting state ($P < 0·01$).

The excretion rate profiles of the free metabolite showed that the maximum excretion rate ($V_{max.}$) was highest following the consumption of the high fat meal (23·8 ± 3·9 mg h^{-1}), followed by that after the low fat meal (17·6 ± 2·2) while the lowest value was obtained with the fasting state (8·8 ± 1·1) (Fig. 2). The differences were significant ($P < 0·01$).

Khalafalla et al (1981) showed that the ingestion of fatty diet (eggs, cream, butter and bread) by five volunteers gave an average of 37% increase in the bioavailability of griseofulvin also measured as 6-DMG excreted in urine. We found an increase of 70% bioavailability following the ingestion of a low fat meal while a high-fat meal gave about 120% increase when compared with the fasting state. The apparent disparity between our work and that of Khalafalla et al (1981) may be due to the amount of food consumed and the total fat content of each meal consumed.

We would like to thank the staff of the Dietetics Department of Ife University Teaching Hospital Complex, Ile-Ife, Nigeria for their technical assistance and one of us (F. A. O.) is indebted to the University of Ife for a research grant No. 1427.AN used for the project.

REFERENCES

Arkley, V., Attenburrow, J., Gregory, G. I., Walker, T. (1962) J. Chem. Soc. 1260–1268

Bates, T. R., Sequeira, J. A. L. (1975) J. Pharm. Sci. 64: 793–797

Crounse, R. G. (1963) Arch. Dermatol. 87: 176–180

Kabasakalian, P., Katz, M., Rosenkrantz, B., Townley, E. (1970) J. Pharm. Sci. 59: 595–600

Khalafalla, N., Elgholmy, Z. A., Khalil, S. A. (1981) Pharmazie 36: H. 10–11

Rowland, M., Riegelman, S. (1973) J. Pharm. Sci. 62: 2030–2032

Snedecor, G. W., Cochran, W. G. (1967) Statistical methods, 6th Ed., pp 258–298. Iowa State Press, Ames, Iowa

Steel, R. G. D., Torrie, J. H. (1960) Principles and Procedures of Statistics, pp 99–131. McGraw-Hill Book Company, Inc., Toronto