THE INFLUENCE OF SEX ON THE CATABOLISM OF GRISEOFULVIN

By Dorothy Busfield, K. J. Child, B. Basil and E. G. Tomich

From Glaxo Laboratories Limited, Greenford, Middlesex

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Blood griseofulvin levels have been determined on rats given a single oral, subcutaneous, intraperitoneal or intravenous dose and on guinea pigs and human volunteers after oral administration. In rats the blood levels of females were higher than those of males: this applied to all four routes of administration. No differences in blood levels between males and females were observed in guinea pigs or human volunteers. *In vitro* studies have shown that liver slices obtained from male rats destroy griseofulvin more rapidly than those from females; the sex difference did not apply to rabbits or guinea pigs.

The influence of sex on the toxicities and pharmacological activities of some drugs is well recognised and has been reviewed recently[1]. This influence, however, is often found to apply only to a single species. In some instances its dependence on hormones has been demonstrated[2–7].

In earlier studies on the biological disposition of griseofulvin, we observed that the blood levels obtained after oral dosing were higher in female albino rats (WAG strain) than in males. We decided to investigate this finding further and to extend our studies to another strain of rats and to other species.

Materials and Methods

Estimation of Griseofulvin

Blood samples and solutions from the liver-incubation experiments were assayed in duplicate by the spectrophotofluorometric method of Bedford, Child and Tomich[8]. Blood samples (3 to 5 ml.), were obtained from anaesthetised rats and guinea pigs by direct cardiac puncture and from human volunteers by venipuncture. Heparin, 50 I.U. in 0·1 ml. physiological saline to 4 ml. blood, was used to prevent clotting.

Blood Level Experiments

Single 10 mg. tablets of griseofulvin were administered orally to male and female guinea pigs weighing 280 to 320 g., and single oral doses of 1 g. (4 × 250 mg. tablets) to human male and female volunteers. Male and female albino rats, WAG strain, weight range 125 to 175 g., received griseofulvin by the oral, intraperitoneal, subcutaneous or intravenous route. The doses used, mg./kg., were 50 and 100 orally, 25 intraperitoneally, 100 subcutaneously and 20 intravenously. The griseofulvin was presented orally or intraperitoneally as an aqueous suspension in 0·5 per cent Tween 80, subcutaneously as a suspension in arachis oil and intravenously as a solution in 75 per cent *NN*-dimethylformamide.

TABLE I

BLOOD GRISEOFULVIN LEVELS IN MALE AND FEMALE RATS GIVEN SINGLE DOSES BY THE ORAL, INTRAVENOUS, SUBCUTANEOUS OR INTRAPERITONEAL ROUTE

(each value is the mean ± S.E.* for 6 rats)

Route	Dose mg./kg.	Sex	Hours after administration												
			1/12	¼	½	1	2	3	4	5	6	7	8	12	16
			Blood griseofulvin concentrations (μg./ml.)												
Oral	50	male	—	—	—	—	0·9 ± 0·1	—	1·3 ± 0·3	—	0·7 ± 0·1	—	0·6 ± 0·1	0·1	0
		female	—	—	—	—	1·9 ± 0·2	—	2·3 ± 0·1	—	2·2 ± 0·3	—	1·7 ± 0·2	0·2	0·1
	100	male	—	—	—	—	1·7 ± 0·2	—	2·5 ± 0·6	—	1·7 ± 0·2	—	2·1 ± 0·4	0·6 ± 0·4	0
		female	—	—	—	—	2·4 ± 0·2	—	3·8 ± 0·3	—	2·9 ± 0·2	—	2·4 ± 0·2	0·8 ± 0·1	0·2
Intra-venous	20	male	7·6 ± 0·4	5·6 ± 0·3	4·3 ± 0·3	3·0 ± 0·6	1·4 ± 0·4	0·4 ± 0·1	0·1	—	—	—	—	—	—
		female	10·2 ± 0·4	7·6 ± 0·6	5·4 ± 0·3	4·4 ± 0·3	2·5 ± 0·4	1·6 ± 0·3	1·2 ± 0·2	0·9 ± 0·2	0·5 ± 0·1	0·4 ± 0·1	—	—	—
Intraperi-toneal	25	male	0·5 ± 0·1	1·2 ± 0·1	0·7 ± 0·1	0·6 ± 0·1	0·3	0·4 ± 0·2	0·2	—	—	—	—	—	—
		female	0·7 ± 0·1	1·7 ± 0·1	1·7 ± 0·1	1·0 ± 0·1	0·9 ± 0·2	0·8 ± 0·1	0·6 ± 0·1	—	0·4 ± 0·1	—	—	—	—
Subcu-taneous	100	male	—	—	—	—	0·3	0·3	0·4 ± 0·1	—	0·2	—	0·2	—	—
		female	—	—	—	0·7 ± 0·2	0·9 ± 0·1	1·0 ± 0·2	1·5 ± 0·2	—	0·7 ± 0·1	—	0·4 ± 0·1	0·3	—

* Standard errors not quoted for mean values less than 0·4 μg./ml.

Incubation of Griseofulvin with Liver Slices

Albino and piebald rats, WAG and PVG strains, respectively, guinea pigs and rabbits were used in these experiments. The animals were killed by a blow on the head; their livers were immediately removed and placed in ice-cold Krebs's solution. The livers were thinly sliced with a Stadie-Riggs tissue slicer, and approximately 200 mg. of the slices were incubated at 37° for 2 hours with 10 ml. Krebs's solution containing griseofulvin (10 μg./ml.). Immediately before and during incubation the solutions were oxygenated with a mixture of 95 per cent oxygen and 5 per cent carbon dioxide. After 2 hours incubation the fluids were decanted and their griseofulvin contents determined. The liver slices were blotted dry and weighed. The results are expressed as amounts of griseofulvin destroyed by 200 mg. of liver in 2 hours.

RESULTS

Blood Levels in Rats

The blood levels of griseofulvin at various times after a single oral dose are given in Table I. At both dose levels, 50 and 100 mg./kg., the female rats gave higher and more prolonged blood levels than the males; the lower dose in females and the higher dose in males gave approximately equal blood levels.

It has previously been shown that griseofulvin disappears rapidly from the blood of male rats after intravenous injection[9]. The blood levels of griseofulvin in male and female rats after a single intravenous dose are given in Table I. Again the females gave higher and more prolonged levels than the males.

Blood levels after subcutaneous injection of the arachis oil suspension and after intraperitoneal injection of the aqueous suspension are also given in Table I. Griseofulvin was not detectable in the blood after a subcutaneous injection of an aqueous suspension at a dose of 100 mg./kg., whereas this dose of the drug in arachis oil gave measurable levels lasting for several hours. Griseofulvin was absorbed rapidly after intraperitoneal injection of 25 mg./kg., peak levels being attained in 15 to 30 minutes. As after oral dosing, the blood levels after subcutaneous or intraperitoneal injection were higher in the female rats than in the males.

Blood Levels in Guinea Pigs and Human Volunteers

Blood griseofulvin levels obtained in guinea pigs and human volunteers given single oral doses are shown in Figures 1 and 2. There were no differences in the blood levels of male and female guinea pigs. In both sexes peak values were reached at 3 hours: at 24 hours griseofulvin was no longer detectable (Fig. 1).

In the human volunteers peak levels were attained in 4 hours, and griseofulvin was still detectable 26 hours after dosing. After a single oral dose of 1 g. there were no differences in blood levels between men and women. These results are shown in Figure 2.

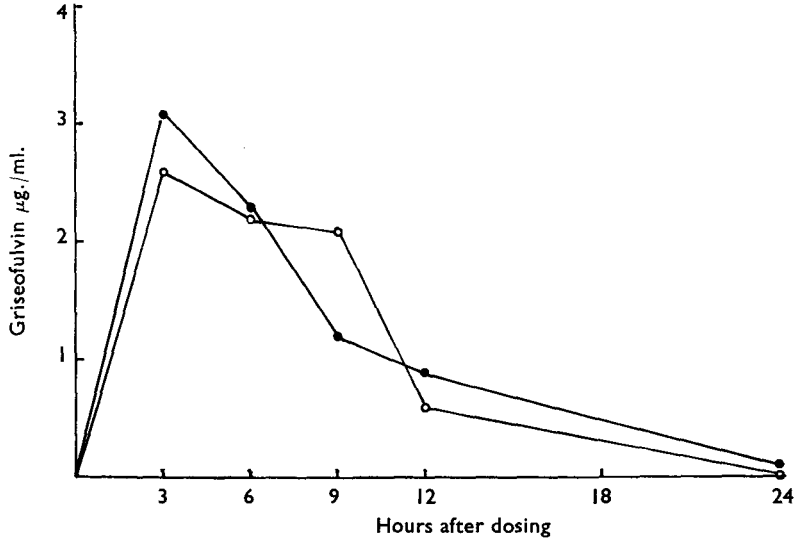

FIG. 1. Blood griseofulvin levels in guinea pigs after a single oral dose of 33 mg./kg. Each point is the mean for three animals.

Female = O—O Male = ●—●

Incubation of Griseofulvin with Liver Slices

The results obtained are given in Table II. Liver slices from adult male WAG rats destroyed griseofulvin more rapidly than those from adult females of the same strain ($P < 0.001$). Similar but less significant differences between males and females were obtained with weanlings of the same strain ($P < 0.02$) and with adult rats of the PVG strain ($P < 0.02$).

No sex differences were recorded in the rates of griseofulvin catabolism when the livers of rabbits or guinea pigs were used.

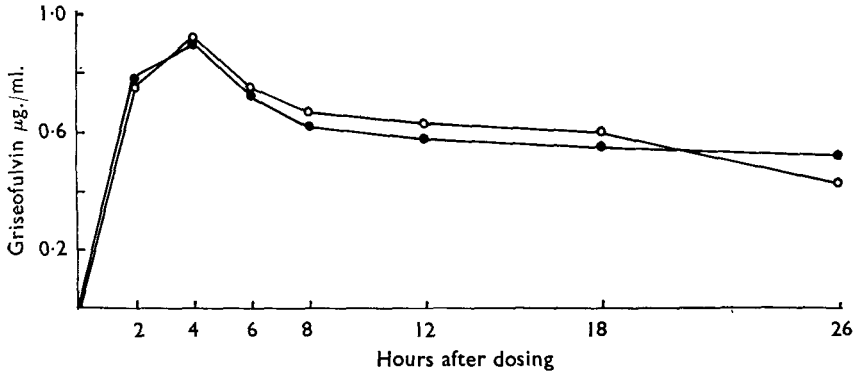

FIG. 2. Blood griseofulvin levels in human volunteers after a single oral dose of 1 g. Each point is the mean for six volunteers.

Female = O—O Male = ●—●

TABLE II

In vitro CATABOLISM OF GRISEOFULVIN BY LIVER SLICES

Species and strain	μg. griseofulvin destroyed in 2 hours by 200 mg. liver		Probability of difference between males and females being due to chance
	Male	Female	
Adult WAG rats	55·4 ± 2·8* (21)†	36·2 ± 2·7 (21)	$P < 0.001$
Weanling WAG rats	57·7 ± 2·8 (6)	45·7 ± 2·7 (6)	$P < 0.02$
Adult PVG rats	49·2 ± 4·6 (5)	32·8 ± 4·6 (5)	$P < 0.02$
Adult rabbits	42·5 ± 5·4 (8)	48·4 ± 7·6 (8)	$P > 0.5$
Adult guinea pigs	45·3 ± 0·8 (6)	47·8 ± 4·2 (6)	$P > 0.5$

* Standard error. † Number of observations.

DISCUSSION

The experiments described above show that female rats have higher blood griseofulvin levels than males, and this difference can be observed after either oral or parenteral administration. Presumably the difference does not arise from different degrees of gastrointestinal absorption. The results of the parenteral experiments, particularly those by the intravenous route, suggest that the differences in blood level between the two sexes reflect different rates of catabolism.

The results of the *in vitro* experiments are consistent with this view. In common with other drugs showing differences in toxicity or pharmacological activity between the sexes, griseofulvin appears to show this difference in only one species, in this instance the rat.

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