International Journal of Pharmaceutics, 33 (1986) 235–242
Elsevier

IJP 01124

Gastrointestinal absorption of griseofulvin from liquid organic acids and esters in rats

Syachruddin Kadir, Teruo Murakami, Yutaka Higashi and Noboru Yata

Institute of Pharmaceutical Sciences, Hiroshima University School of Medicine, Hiroshima (Japan)

(Received 25 March 1986)
(Modified version received 9 June 1986)
(Accepted 10 June 1986)

Key words: Griseofulvin – Gastrointestinal absorption – Ethyl acetoacetate – Methyl propionate – Methyl caproate – Emulsion – Absorption promoter – Gastric emptying time

Summary

Griseofulvin was administered to rats in the dosage form of an aqueous suspension, a corn oil-in-water emulsion, or a solution of liquid organic acids and esters and the absorption characteristics of griseofulvin following its oral, intraduodenal or intragastric administration were compared. The extent of absorption of griseofulvin was markedly enhanced when administered orally as either a solution of ethyl acetoacetate, methyl propionate, or methyl caproate. Greatest absorption was observed in the methyl propionate solution. The absorption result of the methyl propionate solution was higher than that of an aqueous suspension when evaluated by AUC and C_{max}. It was also found that ethyl acetoacetate enhanced mainly the gastric absorption of griseofulvin and methyl propionate and methyl caproate enhanced the intestinal absorption of griseofulvin. The effect of the vehicles on the gastric emptying process of griseofulvin and gastrointestinal mucosal damage was also investigated. A strong inhibitory effect on the gastric emptying process of griseofulvin was observed following oral administration of emulsion, methyl propionate or methyl caproate solution. Gastrointestinal mucosal damage was not observed in any of the cases. Some discussions are also presented.

Introduction

Griseofulvin is an antifungal antibiotic having a very low solubility in water and also in hydrocarbons (Elworthy and Lipscomb, 1968). The low water solubility causes the slow absorption from the GI tract (Crounse, 1961, 1963). Bates and Carrigan (1975) reported that griseofulvin is apparently absorbed in a zero-order fashion from an aqueous suspension and/or an oil-in-water emulsion because of a slow, rate-determining dissolution step. This kinetic zero-order absorption is considered to be derived from the extraordinarily low water solubility of griseofulvin in the GI tract (Bates and Carrigan, 1975). As a result, the absorption of griseofulvin from the GI tract is erratic both inter-subject and intra-subject, and is sometimes incomplete for clinical cure (Aoyagi et al., 1982, 1984). For these reasons, many studies have been reported regarding an increase in the bioavailability of griseofulvin (Chiou and Riegelman, 1971; Bloedow and Hayton, 1976).

In order to get rapid and complete absorption of griseofulvin in animals and humans, micronized and ultramicronized griseofulvin was developed commercially. However, micronized griseofulvin is

Correspondence: N. Yata, Institute of Pharmaceutical Sciences, Hiroshima University School of Medicine, 1-2-3 Kasumi, Minami-Ku, Hiroshima 734, Japan.

still slowly absorbed after its oral administration by fasting subjects (Rowland et al., 1968; Lin and Symchowicz, 1975; Straughn et al., 1980). Carrigan and Bates (1973) developed an emulsion dosage form of griseofulvin based on the fact that the absorption of regular and micronized griseofulvin was markedly enhanced by coadministration with meals high in fat or triglyceride content in animals and humans (Kraml et al., 1962; Bloedow and Hayton, 1976; Kabasakalian et al., 1970). To date, the oil-in-water emulsion dosage form is reported as the best delivery dosage form for griseofulvin (Carrigan and Bates, 1973; Bates and Sequeria, 1975).

Recently, in a study on solubility behavior of griseofulvin using fatty acids, Grant and Abougela (1982) reported that griseofulvin is easily dissolved in various alkanoic acids with heating. However, no in vivo information has yet been reported on the absorption of griseofulvin from various organic acid solutions.

In the present study using rats, the usefulness of various liquid organic acids and esters as vehicles for oral dosage forms of griseofulvin were examined with the aim of improvement in bioavailability of griseofulvin.

Materials and Methods

Materials

The griseofulvin used in the present study was purchased from Sigma Chemical Co. and was used after passing through a 145 mesh screen (less than 105 μm). The following liquid organic acids and their esters of analytical grade were purchased from Wako Pure Chemical Ind., and Tokyo Kasei and were used as vehicles for griseofulvin: acetic acid, ethyl acetoacetate, lactic acid, ethyl lactate, methyl propionate, ethyl pyruvate, butyric acid, caproic acid, methyl caproate, capric acid, and oleic acid. Each vehicle was used without further purification. All other reagents were of the finest grade available.

Determination of solubility

The solubility of griseofulvin in water and in each of the liquid acids and esters was determined at 37°C. Each solvent (5–6 ml) was mixed with a sufficient amount of griseofulvin in a test tube, and the mixture was sonicated for 10 min with the aid of an ultrasonic bath in order to facilitate the rate of dissolution of griseofulvin. After standing for 24 h at 37°C, the supernatant was filtered through a membrane filter (Millipore, FH 0.5 μm). The concentration of the griseofulvin in the filtrate was determined using HPLC.

Dosage forms

Three dosage forms were subjected to in vivo absorption experiments. The first one was an aqueous suspension containing 25 mg of griseofulvin in 1 ml of 1% sodium carboxymethyl cellulose aqueous solution. The second one was an oil-in-water emulsion, which was prepared according to the method of Carrigan and Bates (1973) with some modifications: a mixture containing 20 mg of griseofulvin, 20 mg of polysorbate 80, 20 mg of sesame oil, 0.4 ml of corn oil, and a sufficient quantity of distilled water to make up to 1 ml was subjected to sonication for 5 min to make an emulsion. The aqueous suspension and emulsion were again subjected to sonication in an ultrasonic bath (Branson, B-22OH) for 10 min prior to the absorption experiments. The third dosage form was an organic acid and ester solution. Griseofulvin was dissolved in each acid and ester with heating. The resulting solution was clear even after cooling down to room temperature for at least 20 min.

Absorption studies

Male Wistar rats, 200–230 g, were used. Rats were fasted for 15 h prior to and during the absorption experiments, but allowed free access to water.

(1) Oral administration

The aqueous suspension, emulsion and solutions were orally administered to conscious rats using a metallic stomach tube at a dose of 50 mg of griseofulvin/kg. The dosed volumes were 2.5 ml/kg for emulsion and 2.0 ml/kg for aqueous suspension and acid/ester solutions. After dosing, each animal was placed in a restraining cage.

(2) Intraduodenal administration

The animals were anesthetized lightly by inhalation of ethyl ether. The stomach was exposed by a midline abdominal incision and the bile duct was ligated. Polyethylene tubing (PE 50) was inserted from a small incision made on the stomach in the direction of the duodenum. A griseofulvin solution or suspension was introduced into the duodenum via the polyethylene tubing at a dose of 50 mg of griseofulvin/kg. The dosed volumes were the same as those of oral administration. Immediately after administration, ligation was made at the pylorus to prevent leaking of the solution or suspension into the stomach. After closing the abdomen, each animal was placed in a restraining cage.

Approximately 0.3 ml blood samples were collected from the jugular vein with a heparinized-syringe at 1, 2, 4, 6, 8 and 10 h after oral and intraduodenal administrations. Plasma samples were used for the assay of griseofulvin.

(3) Intragastric administration

Rats were anesthetized by intraperitoneal injection of pentobarbital and kept supine on a surface controlled at 37°C to maintain normal body temperature during experiments. The stomach was exposed by a midline abdominal incision and the pylorus was ligated. After closing the abdomen, griseofulvin solution or suspension was administered to the stomach using a stomach tube at a dose of 50 mg/kg. Ligation of the cardiac orifice was made 1 h after administration. Immediately after ligation, the rat was killed by decapitation and the stomach was removed. A blood sample was also collected at the same time. The inside of the stomach was washed out with a sufficient quantity of 50% methanol–aqueous solution. The washings were all combined together and made up to 100 ml with a 50% methanol–aqueous solution. The amount of griseofulvin absorbed was calculated from the unabsorbed amount observed in the washings.

An assessment of gastrointestinal mucosal damage

An assessment of gastrointestinal mucosal damage was performed according to the method of Nakamura et al. (1982, 1984). At 0, 1, 4 or 15 h following oral administration of either of ethyl-acetoacetate, methyl propionate or methyl caproate at the dose of 2 ml/kg, the rats received phenol red at a dose of 2 μmol/2 ml of saline/kg by gastric intubation. After intubation, each rat was placed in a metabolic cage, and the urine was collected for 8 h after administration of phenol red. Phenol red in urine samples was determined spectrophotometrically.

Analytical method

Griseofulvin sample solution (0.1 or 0.05 ml) was acidified with 1 ml of 0.3 N HCl and extracted with 7 ml of hexane. Five ml of the organic phase was evaporated to dryness under reduced pressure. The residue was dissolved in 100 μl methanol containing diclofenac sodium salt as an internal standard at a concentration of 5 μg/ml or 10 μg/ml and 5 μl of the solution was used for HPLC assay. The HPLC was carried out with the HPLC UV8 (Toyo soda, Model II) apparatus equipped with a UV detector and a (TSK-Gel Toyo Soda, ODS-120T) reverse phase column. Elution was done with 0.1 M acetic acid–acetonitrile (4:6 v/v) at ambient temperature and the flow rate was 1 ml/min. The eluted griseofulvin and diclofenac were detected by measuring their UV absorption at 294 nm. The retention times of griseofulvin and diclofenac were 5.9 min and 9.0 min, respectively.

Phenol red in the urine samples was determined spectrophotometrically. After alkalinization with 1 N NaOH, urine samples were diluted with distilled water appropriately, and determined spectrophotometrically at 560 nm.

Statistical analysis of the results was performed by using Student's *t*-test.

Results and Discussion

Solubility of griseofulvin in various vehicles

In order to find vehicles in which griseofulvin could be dissolved easily, the solubility of griseofulvin at 37°C was determined using some organic liquid vehicles. The solubility of griseofulvin is summarized in Table 1. The solubility of griseofulvin in various organic vehicles was found to be

TABLE 1

SOLUBILITY OF GRISEOFULVIN AT 37°C

Vehicle	Solubility (g/100 ml)
Water	0.0011
Acetic acid	4.451
Ethyl acetoacetate	3.971
Lactic acid	2.704
Ethyl lactate	2.452
Methyl propionate	1.649
Ethyl pyruvate	3.715
Butyric acid	1.279
Caproic acid	2.144
Methyl caproate	0.378
Capric acid	0.378
Oleic acid	0.325

much higher than that in water. The solubility of griseofulvin in short-chain fatty acids was found to be higher than that in longer-chain fatty acids. And it was also observed that the solubility of griseofulvin in organic liquid vehicles increased markedly with heating as reported by Grant and Abougela (1982).

Oral administration of griseofulvin in rats

The absorption characteristics of orally administered griseofulvin from the vehicles listed in Table 1 was assessed in rats as compared to those from either an aqueous suspension or a corn oil-in-water (o/w) emulsion which was developed by Carrigan and Bates (1973).

The results are listed in Table 2 in terms of area under the concentration–time curve (AUC), peak plasma level (C_{max}) and the time required to reach the C_{max} (T_{max}). As shown in Table 2, the extent of absorption of griseofulvin was significantly increased by administering the drug as a solution of ethyl acetoacetate, methyl propionate, methyl caproate and as an emulsion as compared to an aqueous suspension. In particular, the extent of absorption of griseofulvin from methyl propionate solution was 1.7 times higher than that of emulsion when evaluated by AUC. On the other hand, the absorption of griseofulvin was not increased by administering the drug dissolved in the other vehicles such as alkanoic acids tested in the present study, although griseofulvin was administered as a solution.

TABLE 2

AUC_{0-10}, C_{max} AND T_{max} OF GRISEOFULVIN AFTER ORAL ADMINISTRATION IN RATS

Vehicle	AUC ($\mu g \cdot h/ml$)	C_{max} ($\mu g/ml$)	T_{max} (h)
Aqueous suspension	2.28 ± 0.67	0.46 ± 0.10	2.0
Emulsion	6.78 ± 0.40 [a]	1.48 ± 0.54 [a]	4.0
Acetic acid	1.09 ± 0.04	0.23 ± 0.07	2.0
Ethyl acetoacetate	7.84 ± 0.33 [a]	1.47 ± 0.14 [a]	1.0
Lactic acid	1.32 ± 0.98	0.37 ± 0.36	3.3
Ethyl lactate	1.58 ± 0.33	0.47 ± 0.25	1.7
Methyl propionate	11.42 ± 1.78 [a]	3.88 ± 0.18 [a]	4.0
Ethyl pyruvate	1.70 ± 0.59	0.70 ± 0.54	1.3
Butyric acid	3.44 ± 0.43	0.42 ± 0.07	2.0
Caproic acid	2.34 ± 0.58	0.50 ± 0.27	4.3
Methyl caproate	6.51 ± 2.10 [a]	1.31 ± 0.73 [a]	4.0
Capric acid	1.05 ± 0.85	0.22 ± 0.11	5.3
Oleic acid	0.96 ± 0.95	0.62 ± 0.83	8.0

[a] Significantly different from aqueous suspension, $P < 0.05$.
Dose of griseofulvin: 50 mg/kg.
Each value represents the mean ± S.D. ($n = 3$–4).

This result indicates that the enhanced absorption of griseofulvin administered as ethyl acetoacetate, methyl propionate or methyl caproate solution is not due only to the dosage form which was as a solution. The concentration of griseofulvin in plasma as a function of time after oral administration of drug dissolved in ethyl acetoacetate, methyl propionate and methyl caproate is shown in Fig. 1 together with the results of aqueous suspension and o/w emulsion. Fig. 1 indicates that the griseofulvin was absorbed at a faster rate from the ester solutions than from the aqueous suspension, although their T_{max}'s were markedly delayed except in the case of ethyl acetoacetate.

Intraduodenal administration of griseofulvin

In order to avoid the effects of the gastric emptying process and to examine the absorption characteristics of griseofulvin in the intestine, griseofulvin was administered directly into the duodenum of bile duct-ligated rats as a solution of ethyl acetoacetate, methyl propionate, methyl

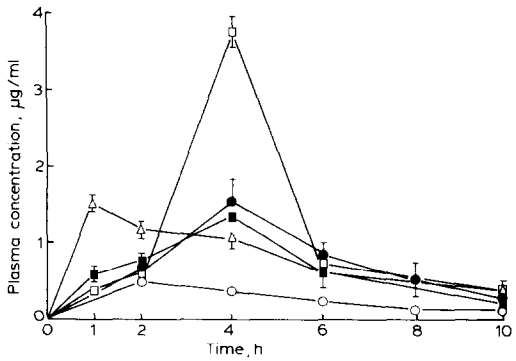

Fig. 1. Plasma concentration of griseofulvin after oral administration in rats. ○, aqueous suspension; ●, emulsion; △, ethyl acetoacetate; □, methyl propionate; ■, methyl caproate. The error bars represent the S.D. with $n = 3$–4. Dose of griseofulvin: 50 mg/kg.

caproate, or as an emulsion which showed a marked enhancement in absorption after oral administration.

The plasma concentration–time profile of griseofulvin is shown in Fig. 2. The resultant AUC, C_{max} and T_{max} after intraduodenal administration are summarized in Table 3. A similar enhanced absorption of griseofulvin was observed after administration of methyl propionate solution, methyl caproate solution and emulsion as compared to the aqueous suspension, although the magnitude of the enhancement was reduced. The T_{max}'s were shorter than those after oral administration except in the case of ethyl acetoacetate. These observations suggest that the enhanced oral absorption after administering the drug dissolved in methyl caproate or methyl propionate could be attributed to the enhanced intestinal absorption, and the delayed T_{max}'s in oral administration could result from the delayed gastric emptying time of griseofulvin caused by the vehicle.

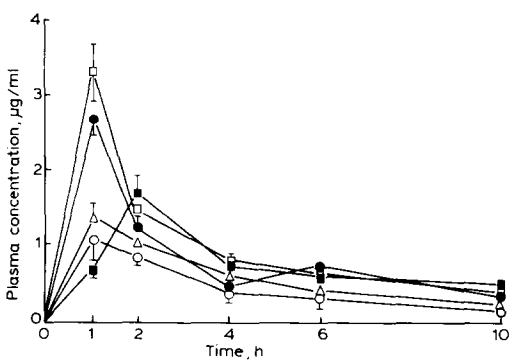

Fig. 2. Plasma concentration of griseofulvin after intraduodenal administration in rats. ○, aqueous suspension; ●, emulsion; △, ethyl acetoacetate; □, methyl propionate; ■, methyl caproate. The error bars represent the S.D. with $n = 3$–4. Dose of griseofulvin: 50 mg/kg.

TABLE 3

AUC_{0-10}, C_{max} AND T_{max} OF GRISEOFULVIN AFTER INTRADUODENAL ADMINISTRATION IN RATS

Vehicle	AUC (μg·h/ml)	C_{max} (μg/ml)	T_{max} (h)
Aqueous suspension	4.62 ± 2.39	1.08 ± 0.58	1.0
Emulsion	7.88 ± 1.03 [a]	2.67 ± 0.40 [a]	1.0
Ethyl acetoacetate	5.66 ± 0.98	1.35 ± 0.38	1.0
Methyl propionate	9.61 ± 0.54 [a]	3.26 ± 0.81 [a]	1.0
Methyl caproate	7.31 ± 1.28 [a]	1.67 ± 0.52 [a]	2.0

[a] Significantly different from aqueous suspension, $P < 0.05$. Dose of griseofulvin: 50 mg/kg.
Each value represents the mean ± S.D. ($n = 3$–4).

It is interesting to note that the ethyl acetoacetate solution of griseofulvin did not show a clear increase in the extent of absorption after intraduodenal administration as after oral administration. Two possible reasons that could explain this result concerning the different effect of ethyl acetoacetate are as follows: (a) ethyl acetoacetate could have enhanced the intestinal absorption of griseofulvin only in the presence of bile juice; and (b) ethyl acetoacetate could have enhanced the absorption of griseofulvin in the stomach.

At first, the possibility of (a), the effect of bile on the absorption of griseofulvin dissolved in ethyl acetoacetate was investigated by intraduodenal administration of ethyl acetoacetate solution using rats without bile duct ligation (non-ligated rat). The plasma level of griseofulvin in non-ligated rats was compared to that in bile duct-ligated rats. However, no difference was observed in plasma level of griseofulvin after intraduodenal administration between non-ligated rats and bile duct-ligated rats. It has been reported that the presence of emulsified corn oil in the intestinal tract stimulates bile secretion (Holt, 1972; Carey and Small, 1972) and that the stimulated bile plays a role in

increased dissolution rate of griseofulvin in the intestinal fluid (Bates et al., 1967) resulting in the increase of bioavailability of this poorly soluble antibiotic. In the cases of methyl propionate and methyl caproate, a marked enhancement in the intestinal absorption of griseofulvin was observed in the absence of bile juice (bile duct-ligated rats) as shown in Fig. 2 and Table 3. Based on these findings, the contribution of bile juice to the enhancement in absorption of griseofulvin from ethyl acetoacetate, methyl propionate or methyl caproate solution could be ruled out.

The other possibility (b) was examined through gastric absorption experiments.

Gastric absorption of griseofulvin

Effects of vehicles on the gastric absorption of griseofulvin were investigated. Griseofulvin dissolved in each of ethyl acetoacetate, methyl propionate or methyl caproate was directly administered into pylorus-ligated rat stomach, and the absorption percent from stomach was estimated by measuring the remaining amount of griseofulvin in the stomach 1 h after administration. The plasma concentration of griseofulvin was also measured at the same time. The results of percent absorption and plasma level are shown in Fig. 3.

The gastric absorption of griseofulvin from ethyl acetoacetate solution was significantly enhanced as compared to that from aqueous suspension and other solutions. The enhanced gastric absorption of griseofulvin by ethyl acetoacetate was also confirmed from its plasma level. On the other hand, the gastric absorption of griseofulvin was not enhanced by methyl propionate or methyl caproate.

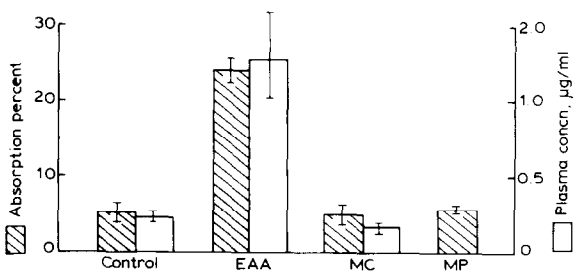

Fig. 3. Gastric absorption of griseofulvin after administration into ligated stomach of rats. The error bars represent the S.D. with $n = 3$–4. Dose of griseofulvin: 50 mg/kg.

These results suggest that the enhanced absorption of griseofulvin and the short T_{max} after oral administration of ethyl acetoacetate solution could be attributed to the enhanced gastric absorption.

The effect of vehicle on the gastric emptying time

When griseofulvin was administered orally as either a solution of methyl propionate, methyl caproate or as an emulsion, their T_{max}'s were delayed as compared to that of an aqueous suspension. T_{max}'s were found to be short after intraduodenal administrations compared to those after oral administrations. These results suggest that the vehicles such as methyl propionate, methyl caproate, and emulsion may have delayed the gastric emptying time (GET) of griseofulvin. Hunt (1983) also reported that fatty acids and their related compounds such as ethyl oleate slowed gastric emptying.

The inhibitory effect of vehicle on the GET was investigated by measuring the amount of griseofulvin remaining in stomach at an appropriate time interval after oral administration. The percent of dose remaining in stomach was plotted as a function of time as shown in Fig. 4. The times required for emptying 75% of dose were 1 h for aqueous suspension and ethyl acetoacetate solution, 2 h for emulsion, and more than 3 h for methyl propionate and methyl caproate solutions, respectively. However, as described earlier, griseofulvin was absorbed from the stomach upon

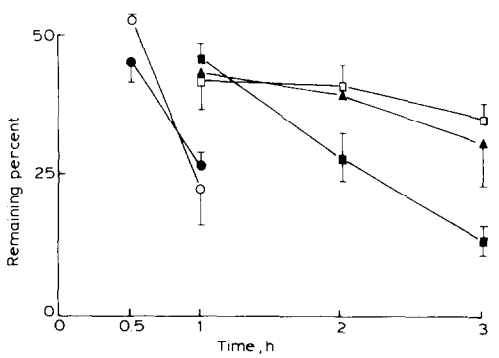

Fig. 4. Remaining percent of griseofulvin in stomach after administration into stomach in rats. ○, aqueous suspension; ■, emulsion; ●, ethyl acetoacetate; □, methyl propionate; ▲, methyl caproate. The error bars represent the S.D. with $n = 3$. Dose of griseofulvin: 50 mg/kg.

administration of the ethyl acetoacetate solution. So, the GET estimated from amount of the drug remaining in the stomach following gastric administration of ethyl acetoacetate solution involves both emptying due to direct absorption of griseofulvin from the stomach and emptying due to the transfer from the stomach to the duodenum. On the other hand, the absorption of griseofulvin dissolved in other vehicles from the stomach was very low and negligible as shown in Fig. 3. This means that the GET estimated from amount of the drug remaining in the stomach following administration of griseofulvin in aqueous suspension, emulsion, methyl propionate, or methyl caproate solution reflects correctly the emptying of griseofulvin from stomach to intestinal tract.

Bates and Sequeira (1975) reported the enhancement in the bioavailability of griseofulvin in humans when administered as an emulsion dosage form. As the mechanism, they proposed both the inhibitory effect of lipid (emulsified corn oil) on the gastric emptying process and stimulated bile secretion in the presence of emulsified corn oil in the intestinal tract.

In the present study, the inhibitory effect of the present vehicles on the GET was also observed following oral administration of methyl propionate or methyl caproate solution. However, emulsion, methyl propionate and methyl caproate showed a marked enhancement even in the case of intraduodenal administration. Therefore, our results cannot be explained fully with the mechanisms proposed by Bates and Sequeira (1975).

Another reason should be raised.

An assessment of gastrointestinal mucosal damage

In order to confirm the contribution of gastrointestinal mucosal damage to the enhancement of gastrointestinal absorption of griseofulvin by administering the drug dissolved in ethyl acetoacetate, methyl propionate, or methyl caproate, an assessment of gastrointestinal mucosal damage by those vehicles was performed according to the method of Nakamura et al. (1982, 1984). The assessment method was based on the following facts. The permeability of the gastrointestinal wall barrier to phenol red, a poorly absorbed drug, is increased by gastrointestinal mucosal damage such as ulcer formation, and good correlation is observed between the extent of gastric damage and urinary excretion of phenol red (Nakamura et al., 1982, 1984). In the present study, each vehicle was administered orally at a dose of 2 ml/kg to 15 h-fasted rats. At 0, 1, 4 or 15 h post-administration of each vehicle, phenol red was administered as an aqueous solution and urinary recovery percent of phenol red was determined for 8 h after administration of phenol red.

The results are shown in Table 4. In the case of 15 h-pretreated rats in Table 4, the urinary recovery percents of phenol red in control rats was higher than those of the other cases. This increase in urinary recovery of phenol red was considered to be due to the long fasting time (30 h, initial fasting time prior to administration of vehicle plus the time prior to administration of phenol red). However, in all cases, there was no difference in urinary recovery percent of phenol red between the group of saline and the groups of other vehicles.

These results indicate that the enhanced gastrointestinal absorption of griseofulvin by administering the drug dissolved in either of ethyl acetoacetate, methyl propionate or methyl caproate is not due to the gastrointestinal mucosal damage such as ulcers.

As a conclusion, the gastrointestinal absorption

TABLE 4

URINARY RECOVERY IN 8 h OF PHENOL RED IN RATS ORALLY PRETREATED WITH VARIOUS VEHICLE

Vehicle	Recovery, %			
	0 h [a]	1 h	4 h	15 h
Saline	4.03	–	4.03	7.04
	(0.85)		(0.85)	(0.87)
Ethyl acetoacetate	3.90	4.31	3.62	7.05
	(0.40)	(0.72)	(0.54)	(0.83)
Methyl propionate	4.66	3.40	4.0	6.85
	(0.62)	(0.50)	(0.5)	(0.58)
Methyl caproate	4.21	4.18	4.52	6.0
	(0.76)	(0.38)	(0.14)	(1.6)

Each value represents the mean (S.D.) ($n = 3$). Each vehicle was administered at the dose of 2 ml/kg.

[a] Time after orally pretreated of vehicle.

of griseofulvin after oral administration was markedly enhanced by administering the drug dissolved in either an emulsion, ethyl acetoacetate, methyl propionate or methyl caproate. Methyl propionate solution gave the highest results and the enhancing effect was higher than that of the emulsion. However, the difference in the site of promoting action of vehicle was found among them, that is, ethyl acetoacetate enhanced the gastric absorption of griseofulvin, whereas methyl propionate and methyl caproate enhanced the intestinal absorption of griseofulvin.

Further investigation is necessary to clarify the mechanism of action of the vehicles.

References

Aoyagi, N., Ogata, H., Kaniwa, N. and Ejima, A., Effect of food on the bioavailability of griseofulvin from microsize and PEG ultramicrosize (Gris-PEG) plain tablet. *J. Pharm. Dyn.*, 4 (1982) 120–124.

Aoyagi, N., Ogata, H., Kaniwa, N., Ejima, A., Yasuda, Y. and Tanioka, Y., Bioavailability of griseofulvin from plain tablets in Göttingen minipigs and the correlation with bioavailability in humans. *J. Pharm. Dyn.*, 7 (1984) 7–14.

Bates, T.R. and Carrigan, P.J., Apparent absorption kinetics of micronized griseofulvin after its oral administration single and multiple-dose regimens to rats as a corn oil-in-water emulsion and aqueous suspension. *J. Pharm. Sci.*, 64 (1975) 1475–1481.

Bates, T.R., Lin, S.L. and Gibaldi, M., Solubilization and rate of dissolution of drugs in the presence of physiologic concentration of lysolecithin. *J. Pharm. Sci.*, 56 (1967) 1492–1495.

Bates, T.R. and Sequeira, J.A., Bioavailability of micronized griseofulvin from corn oil-in-water emulsion, aqueous suspension, and commercial tablet dosage forms in humans. *J. Pharm. Sci.*, 64 (1975) 793–797.

Bloedow, D.C. and Hayton, W.L., Effects of lipids on bioavailability of sulfisoxazole acetyl, dicumarol, and griseofulvin in rats. *J. Pharm. Sci.*, 65 (1976) 328–333.

Carey, M.C. and Small, D.M., Micelle formation by bile salts. *Arch. Intern. Med.*, 130 (1972) 506–527.

Carrigan, P.J. and Bates, T.R., Biopharmaceutics of drugs administered in lipid-containing dosage forms I: GI absorption of griseofulvin from an oil-in-water emulsion in the rat. *J. Pharm. Sci.*, 62 (1973) 1476–1479.

Chiou, W.L. and Riegelman, S., Absorption characteristics of solid dispersed and micronized griseofulvin in man. *J. Pharm. Sci.*, 60 (1971) 1376–1379.

Crounse, R.G., Human pharmacology of griseofulvin: the effect of fat intake on gastrointestinal absorption. *J. Invest. Dermatol.*, 37 (1961) 529–533.

Crounse, R.G., Effective use of griseofulvin. *Arch. Dermatol.*, 87 (1963) 176–178.

Elworthy, P.H. and Lipscomb, F.J., A note on the solubility of griseofulvin. *J. Pharm. Pharmacol.*, 20 (1968) 817–824.

Grant, D.J.W. and Abougela, I.K.A., Solubility behaviour of griseofulvin in fatty acids. *J. Pharm. Pharmacol.*, 34 (1982) 766–770.

Holt, P.R., The roles of bile acids during the process of normal fat and cholesterol absorption. *Arch. Intern. Med.*, 130 (1972) 574–583.

Hunt, J.N., Does calcium mediate slowing of gastric emptying by fat in humans? *Am. J. Physiol.*, 244 (1983) G89–G94.

Kabasakalian, P., Katz, M., Rosenkrantz, B. and Townley, E., Parameters affecting absorption of griseofulvin in a human subject using urinary metabolite excretion data. *J. Pharm. Sci.*, 59 (1970) 595–600.

Kraml, M., Dubuc, J. and Beall, D., Gastrointestinal absorption of griseofulvin I. Effect of particle size, addition of surfactants, and corn oil on the level of griseofulvin in the serum of rats. *Can. J. Biochem.*, 40 (1962) 1449–1451.

Lin, C. and Symchowice, S., Absorption, distribution, metabolism, and excretion of griseofulvin in man and animals. *Drug Metab. Rev.*, 4 (1975) 75–95.

Nakamura, J., Takada, S., Ohtsuka, N., Heya, T., Yamamoto, A., Kimura, T. and Sezaki, H., An assessment of gastrointestinal mucosal damage in vivo: enhancement of urinary recovery after oral administration of phenolsulfonphthalein in ulcer rats. *Chem. Pharm. Bull.*, 30 (1982) 2291–2293.

Nakamura, J., Takada, S., Ohtsuka, N., Heya, T., Ueda, S., Hamaura, T., Yamamoto, A., Kimura, T. and Sezaki, H., An assessment of gastric ulcers in vivo: enhancement of urinary recovery after oral administration of phenolsulfonphthalein in rats. *J. Pharm. Dyn.*, 7 (1984) 485–491.

Rowland, M., Riegelman, S. and Epstein, W.L., Absorption kinetics of griseofulvin in man. *J. Pharm. Sci.*, 57 (1968) 984–989.

Straughn, A.B., Meyer, M.C., Raghow, G. and Rotenberg, K., Bioavailability of microsize and ultramicrosize griseofulvin product in man. *J. Pharmacokin. Biopharm.*, 8 (1980) 347–362.