had dissolved after 15 min. The t_{90} values for the first-order, second-order, and Weibull distribution curves were 30, 11.6, and 19 min, respectively. These results support the utility of the Weibull cumulative distribution equation in the linearization of experimental data.

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Influence of Metoclopramide and Propantheline on GI Absorption of Griseofulvin in Rats

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Abstract □ The effect of metoclopramide and propantheline preadministration on the plasma levels of orally administered griseofulvin was studied. Griseofulvin was administered as an aqueous suspension in 0.5% polysorbate 80 or as a 100% polyethylene glycol 600 solution. Metoclopramide preadministration increased the gastric emptying rate, but propantheline retarded it. The effect on griseofulvin absorption induced by metoclopramide and propantheline was sharply dependent upon the dosage form of griseofulvin administered. When griseofulvin was administered as a suspension dosage form following metoclopramide administration, the griseofulvin peak plasma concentration was reduced by 59% while a concurrent 50% reduction in relative bioavailability was observed. Pretreatment with metoclopramide resulted in a shift of the time required for attainment of the peak plasma griseofulvin concentration. In contrast, metoclopramide administration prior to a dose of griseofulvin dissolved in 100% polyethylene glycol 600 sharply increased both the relative bioavailability and the maximum plasma level of griseofulvin by 234 and 145%, respectively. Propantheline administration prior to a single dose of griseofulvin suspension decreased the maximum plasma level by 30% and delayed the time of its attainment from 5.78 to 19.00 hr with a 50% increase in relative availability. When griseofulvin was administered as a 100% polyethylene glycol solution dosage form, propantheline preadministration reduced both the maximum plasma level and the area under the plasma concentration–time curve by 64 and 44%, respectively.

Keyphrases □ Griseofulvin—GI absorption, effect of metoclopramide and propantheline preadministration, rats □ Metoclopramide—effect of preadministration on GI absorption of griseofulvin, rats □ Propantheline—effect of preadministration on GI absorption of griseofulvin, rats □ Absorption, GI—griseofulvin, effect of metoclopramide and propantheline preadministration, rats □ GI absorption—griseofulvin, effect of metoclopramide and propantheline preadministration, rats □ Antifungal agents—griseofulvin, GI absorption, effect of metoclopramide and propantheline preadministration, rats □ Antiemetics—metoclopramide, effect of preadministration on GI absorption of griseofulvin, rats □ Anticholinergic agents—propantheline, effect of preadministration on GI absorption of griseofulvin, rats

Griseofulvin, a chemically neutral systemic antifungal antibiotic, is commonly used in the treatment of dermatophyte infections in humans (1–4) and domestic animals (5). As a result of inherently poor aqueous solubility (approximately 15 mg/liter at 37°), the drug is slowly, erratically, and incompletely absorbed from the human GI tract (6). However, it is an exceptionally effective antifungal agent after oral administration.

Because griseofulvin is poorly absorbed, it has been used as an investigational model to examine various parameters affecting drug absorption. Its slow and erratic absorption characteristics are the direct result of unusually slow dissolution after oral administration as a solid dosage form. Early experimentation with griseofulvin led to classical observations about the effect of particle-size reduction (7), surfactants (8), and dietary lipids (9) on the absorption of a drug with low solubility and poor availability.

The effects of particle-size reduction (7), micellar solubilization (10), molecular dispersion (11), and emulsification (12) on improving the absorption of poorly absorbed drugs are well recognized. However, far less is known about the effect of GI motility on the absorption of poorly absorbed drugs (13–15). Since griseofulvin is a very poorly soluble drug and its absorption takes place largely in the intestine (16), it was desirable to study the effect of gastric emptying and GI motility on its absorption. Metoclopramide (13) and propantheline (13–15) were used successfully as investigational probes in similar absorption studies to increase or decrease GI motility, respectively.

The purpose of this work is to demonstrate the effect of changes in GI motility on the relative availability of griseofulvin after preadministration of motility-modifying agents.

EXPERIMENTAL

Dosage Forms—Micronized griseofulvin[1] (specific surface area of 1.32 m^2/g) was used in the preparation of two dosage forms. The first preparation was an aqueous suspension containing 25 mg of micronized griseofulvin/ml in 0.5% polysorbate 80 in water. The second preparation was a solution of griseofulvin prepared by dissolving 12.5 mg of drug in

[1] Supplied by Dr. Milo Gibaldi, State University of New York at Buffalo, Buffalo, N.Y.

Table I—Peak Plasma Levels, C_{max} (Micrograms per Milliliter), Time of Occurrence, T_{max} (Hours), and the Area under Plasma Concentration–Time Curves, *AUC* (Micrograms Hour per Milliliter), following Oral Administration of a Micronized Griseofulvin Suspension (100 mg/kg), with Metoclopramide (10 mg/kg) or Propantheline (5 mg/kg) Given Intraperitoneally to the Test Animals 2 hr prior to Griseofulvin Administration

	Control			Metoclopramide Pretreated			Propantheline Pretreated		
	AUC	C_{max}	T_{max}	*AUC*	C_{max}	T_{max}	*AUC*	C_{max}	T_{max}
	37.5	7.35	6	24.9	3.12	4	50.4	3.37	23
	53.0	7.68	5	30.9	4.01	4	41.6	1.78	20
	37.3	6.92	6	19.9	2.50	4	42.3	7.62	23
	37.8	7.02	6	10.5	1.31	2	76.0	1.83	6
	52.9	6.02	6	15.8	2.63	2	42.8	5.42	23
	50.6	6.05	6	27.2	1.90	4	85.7	6.28	20
	45.8	6.60	6	23.5	3.82	2	73.2	4.78	14
	34.1	6.24	6	—	—	—	65.9	6.63	23
	40.4	6.32	5	—	—	—	105.7	—	—
Mean	43.3	6.69	5.78	21.8	2.75	3.14	65.1	4.71	19.00
SE	2.46	0.20	0.15	2.62	0.37	0.40	7.64	0.78	2.15
CV, %	17.1	8.9	7.8	32.0	35.6	33.7	35.3	46.6	32.1
Significance[a]				s	s	s	s	s	s

[a] Determined by Student *t* test; $\alpha = 0.05$ (two tailed), and s = significant.

1 ml of polyethylene glycol 600. A solution containing the same dose as the suspension dosage form could not be prepared due to the limited solubility of griseofulvin in polyethylene glycol 600.

Aqueous solutions of metoclopramide hydrochloride[2] (2.5 mg/ml) and propantheline bromide[3] (1.25 mg/ml) were prepared for intraperitoneal administration. All administered dosage forms were used immediately after preparation.

Plasma Level Studies—Adult male Wistar rats, average weight of 250 g, were fasted for 24 hr prior to and during the experiments. All animals were allowed water *ad libitum* throughout the experiments. Griseofulvin was administered by gastric intubation at constant dose levels of 100 mg/kg (25 mg/250-g rat) with the suspension and of 50 mg/kg (12.5 mg/250-g rat) with the solution.

Different groups of rats were separately injected with either 10 mg of metoclopramide hydrochloride/kg ip or 5 mg of propantheline bromide/kg ip 2 hr prior to oral griseofulvin administration. Control animals received only the respective griseofulvin dosage forms and were included in all experiments.

Blood samples were taken in heparinized tubes from the tail artery of anesthetized rats at suitable time intervals up to 48 hr postdosing. The blood samples were then centrifuged, and the plasma was frozen until assayed.

Gastric Emptying Studies—To evaluate the effect of metoclopramide and propantheline on the gastric emptying rate, single doses of a polyethylene glycol 600 solution or 0.5% polysorbate 80 suspension of griseofulvin were administered orally to the appropriately pretreated rats. Different animals were ether anesthetized at 0, 1, 2, 4, 6, and 11 hr after receiving griseofulvin, the stomach was clamped at the cardiac and pyloric sphincters, and the animal was sacrificed. During the suspension study, a cardiac blood sample was taken immediately prior to sacrifice.

Subsequent to sacrifice, the stomach was excised and homogenized and the homogenate was diluted with distilled water. The amount of griseofulvin in the organ homogenate and, where appropriate, plasma was determined using the procedure utilized for the plasma level studies.

Assay Procedure—A literature method (17) was employed with some modification to determine griseofulvin in biological samples. A 0.01–0.1-ml aliquot of the plasma sample was transferred accurately into a 45-ml polytef-stoppered centrifuge tube containing 5 ml of 0.1 *N* HCl. Anhydrous ether[4], 10 ml, was added to each tube, and the tubes were shaken for 30 min. Then 5 ml of the ether layer was transferred to a 10-ml volumetric flask containing 1 ml of 17.2 μg of diazepam/100 ml of benzene.

The solvent was evaporated to dryness under nitrogen, 1 ml of pesticide grade benzene[5] was added, and 5 μl of the resulting solution was injected into a gas chromatograph[6] equipped with a ^{63}Ni-electron-capture detector. The following conditions were used: glass column, 1.83 m long and 2 mm i.d. packed with 3% OV-25 on 80–100-mesh Chromosorb W; column oven temperature, 285°; injection port temperature, 250°; detector temperature, 350°; and carrier gas (95% argon and 5% methane) flow, 40 ml/min. The injection port configuration permitted on-column injection.

The peak height ratio (griseofulvin–diazepam) method was used to construct a standard curve and to quantitate griseofulvin.

RESULTS AND DISCUSSION

It was reported previously that preadministration of either metoclopramide or propantheline altered the absorption of griseofulvin administered as a suspension in 0.5% polysorbate 80 and as a solution in 100% polyethylene glycol 600 (18, 19). The results of these studies are summarized in Tables I–IV.

Plasma Levels after Oral Suspension of Griseofulvin—Figure 1 depicts representative plasma griseofulvin level–time plots obtained following a single dose of a 100-mg of griseofulvin/kg suspension in control, metoclopramide-predosed, and propantheline-predosed animals.

Pretreatment with metoclopramide, an agent capable of stimulating the gastric emptying reflex and GI motility (13, 18–22), decreased the maximum plasma concentration (C_{max}) by 59% (Table I) while at the same time decreasing the time for attainment of the peak level (T_{max}) by 2.7 hr. The area under the plasma griseofulvin level–time curve (*AUC*) was reduced by 50% (Table I) from controls as a result of metoclopramide preadministration. The observed reduction in the *AUC* for griseofulvin after metoclopramide preadministration is consistent with a 50% reduction in the relative availability of the poorly absorbed antifungal agent.

Alternatively, predosing with propantheline delayed the time for attainment of the maximum plasma griseofulvin level from 5.8 to 19 hr while at the same time increasing the *AUC* by 50% (Table I). These alterations were accompanied by a 30% reduction in the C_{max} for griseofulvin in plasma (Table I).

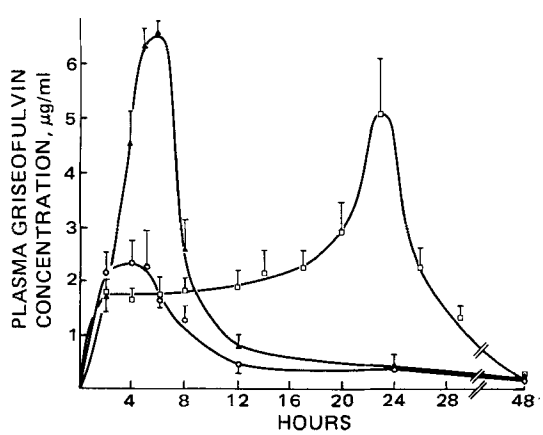

Figure 1—*Plasma griseofulvin concentrations as a function of time following the oral administration of a 100-mg/kg dose of micronized griseofulvin suspension in 0.5% polysorbate 80 to nine control rats* (▲), *seven rats predosed with 10 mg of metoclopramide hydrochloride/kg* (○), *and nine rats predosed with 5 mg of propantheline bromide/kg* (□). *Error bars represent the standard error of the mean.*

[2] Lot L-593-865-01F06, supplied by Merck Sharp and Dohme, West Point, Pa.
[3] Lot 239, supplied by Novopharm Ltd., Toronto, Ontario, Canada.
[4] Analytical reagent grade.
[5] Nanograde, Mallinckrodt.
[6] Hewlett-Packard model 5713A, Avondale, Pa.

Table II—Area under Plasma Concentration–Time Curves, *AUC* (Micrograms Hour per Milliliter), and the Peak Plasma Concentrations, C_{max} (Micrograms per Milliliter), following Oral Administration of Griseofulvin (50 mg/kg) in 100% Polyethylene Glycol 600, with Metoclopramide (10 mg/kg) or Propantheline (5 mg/kg) Given Intraperitoneally to the Test Animals 2 hr prior to Griseofulvin Administration

	Control		Metoclopramide Pretreated		Propantheline Pretreated	
	AUC	C_{max}	*AUC*	C_{max}	*AUC*	C_{max}
	37.6	15.32	126.6	20.34	37.4	5.83
	38.8	13.10	138.6	25.42	27.5	3.87
	55.5	12.01	84.6	22.03	16.4	3.51
	30.1	6.09	142.4	34.81	28.2	3.40
	37.9	11.68	115.0	33.03	17.8	3.40
	41.3	12.33	126.4	25.25	22.6	—
	28.9	8.12	119.4	17.60	13.5	—
	32.6	9.23	158.2	37.20	6.1	—
Mean	37.8	10.98	126.4	26.96	21.2	4.00
SE	2.96	1.05	7.73	2.55	3.46	0.48
CV, %	22.1	27.1	17.3	26.8	46.3	27.0
Significance[a]			s	s	s	s

[a] Determination by Student *t* test; $\alpha = 0.05$ (two tailed), and s = significant.

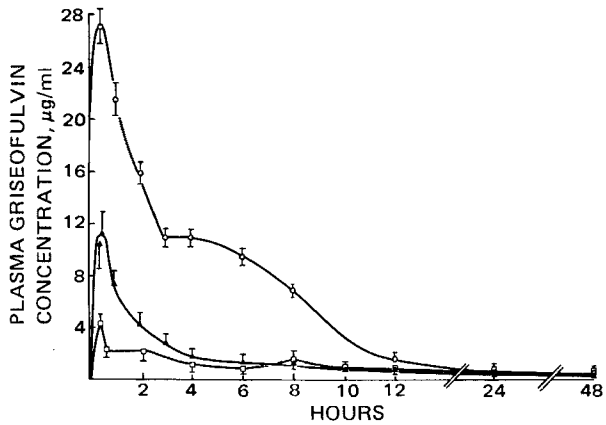

Figure 2—*Plasma griseofulvin concentrations as a function of time following the oral administration of a 50-mg/kg dose of griseofulvin in polyethylene glycol 600 to eight control rats (▲), eight rats predosed with 10 mg of metoclopramide hydrochloride/kg (○), and seven rats predosed with 5 mg of propantheline bromide/kg (□). Error bars represent the standard error of the mean.*

These observations are consistent with the previously observed influences of GI motility modifiers on drug absorption. Metoclopramide was shown to decrease effectively the time for attainment of peak plasma levels of acetaminophen (22) while only slightly influencing the total absorption of this drug. With griseofulvin, a dramatically different situation is encountered since the absorption of this drug is erratic and incomplete (6). Metoclopramide, through its stimulatory influence on the GI tract, decreased the residence time of griseofulvin in the small intestine, resulting in a substantial decrease in total absorption from the less readily available dosage form.

When propantheline was preadministered to rats, the findings were in sharp contrast with the observations after metoclopramide preadministration. Propantheline preadministration markedly increased the relative availability of griseofulvin suspension from controls, presumably through a mechanism similar to that reported with digoxin tablets (13); *i.e.*, an increased residence time in the GI tract allowed additional time for dissolution and subsequent absorption. This observation is consistent with the findings of Bates and Sequeira (15), where propantheline preadministration in humans caused a 1.53-fold increase in the absorption of the antifungal agent administered as an oral suspension.

Plasma Levels after Polyethylene Glycol 600 Solution of Griseofulvin—During the attempt to clarify the effect of motility on griseofulvin absorption, an interesting contrasting interaction between the motility modifiers and griseofulvin was observed when the antifungal agent was administered in polyethylene glycol 600. Figure 2 represents mean plasma griseofulvin level–time plots measured after oral administration of griseofulvin dissolved in 100% polyethylene glycol 600 in control and test rats. Griseofulvin absorption in all cases was rapid, and maximum plasma levels were attained in 20–30 min. With the control rats, the availability of the administered dose after the solution dosage form was nearly twice that observed after the suspension dosage form [(*AUC*) suspension (100 mg/kg) was 43.3 μg hr/ml as opposed to (*AUC*) solution (50 mg/kg) which was 37.8 μg hr/ml] (Tables I and II).

Figure 2 shows the plasma level–time curves of griseofulvin obtained following metoclopramide preadministration to animals receiving griseofulvin dissolved in polyethylene glycol 600. Metoclopramide increased the C_{max} by 145% and the *AUC* by 234% (Table II). Since metoclopramide shortens gastric emptying time and stimulates GI motility (13, 18–22), the absorption of the readily available dissolved drug is enhanced by a more rapid exposure to the proximal small intestine.

In sharp contrast to the observations after metoclopramide preadministration, propantheline reduced the relative availability of griseofulvin administered in solution by 44% (Table II) and decreased the mean peak plasma level by 64% (Fig. 2). This observation was not unexpected since propantheline pretreatment induces a longer residence time of the drug in the stomach where griseofulvin absorption is limited. This delayed drug release to the absorption site may result in either precipitation of the drug or degradation of griseofulvin.

Davis *et al.* (23) noticed a continuous disappearance of griseofulvin from the rat alimentary canal corresponding with the fall in blood level. They attributed this observation to griseofulvin destruction in the gut. However, in this work, addition of 1 ml of distilled water to griseofulvin dissolved in 1 ml of polyethylene glycol 600 caused the drug to precipitate gradually in fine crystals. This observation, coupled with the fact that a large percent of unchanged griseofulvin was recovered from the stomach of the propantheline-pretreated rats 11 hr after griseofulvin administration (Table III), suggests that precipitation rather than destruction may be responsible for the poor relative bioavailability.

In contrast to the observed effect of propantheline on griseofulvin solution, Manninen *et al.* (13) noticed that the absorption properties of digoxin, when given in solution form, were unaffected by treatment with the anticholinergic drug. This difference can perhaps be explained by the different solubility properties of these two drugs; *i.e.*, following administration, with a longer residence time in the stomach, griseofulvin

Table III—Percent Griseofulvin Remaining in Stomach and Corresponding Plasma Levels in the Rat following Oral Administration of Single Doses of 100 mg of Griseofulvin/kg in 0.5% Polysorbate 80 with Test Rats Given Single Doses of Either 10 mg of Metoclopramide Hydrochloride/kg or 5 mg of Propantheline Bromide/kg 2 hr prior to Griseofulvin Administration

Hour Postdosing	Control		Metoclopramide Pretreated		Propantheline Pretreated	
	% in Stomach	Plasma Level, μg/ml	% in Stomach	Plasma Level, μg/ml	% in Stomach	Plasma Level, μg/ml
0	98.4	—	99.3	—	96.0	—
	96.8	—	100.4	—	98.1	—
1	74.2	1.02	20.1	2.74	84.4	0.73
	77.7	1.02	27.7	3.85	89.2	0.83
2	69.6	1.61	32.7	1.44	60.9	1.93
	57.7	0.83	16.4	3.13	89.7	0.99
4	18.7	2.85	7.8	2.07	32.1	4.85
	31.1	3.11	1.6	3.91	31.9	0.89
6	1.9	5.75	0.9	1.01	4.3	0.94
	9.2	2.78	0.5	2.18	28.0	0.75
11	0.2	0.08	0.5	0.01	25.2	2.12
	1.8	0.04	1.4	0.02	47.6	0.21

Table IV—Percent Griseofulvin Remaining in Stomach following Oral Administration of Single Doses of 50 mg of Griseofulvin/kg in Polyethylene Glycol 600 to the Control, Metoclopramide Hydrochloride-Pretreated Rats (10 mg/kg), and Propantheline Bromide-Pretreated Rats (5 mg/kg)

Hour Postdosing	Percent Remaining in Stomach		
	Control	Metoclopramide Pretreated	Propantheline Pretreated
0	98.1	96.5	103.3
	101.3	95.9	96.4
1	86.3	46.7	96.1
	87.8	88.6	97.1
	77.6	50.9	—
2	89.4	44.8	104.3
	65.6	49.0	81.5
	82.9	30.8	96.4
4	56.5	37.5	102.4
	46.9	7.3	74.6
	49.7	41.7	73.0
6	31.4	5.5	68.7
	—	2.6	52.1
	24.6	22.6	—
11	0.0	0.4	49.4
	—	—	54.4
	2.3	1.4	35.1

may precipitate and yield a lower relative availability while digoxin may remain in solution and subsequently be absorbed.

Gastric Emptying—The determination of the amount of griseofulvin remaining in the stomach at different time intervals in control, metoclopramide-predosed, and propantheline-predosed animals lends credence to the speculated effects of the motility modifiers on the gastric emptying pattern obtained after oral griseofulvin administration. The accelerated emptying rate induced by metoclopramide is clearly illustrated by the findings at 1 hr after administration of the griseofulvin suspension; 76% of the suspension dosage form remained in the stomach of control animals while only 24% remained after metoclopramide preadministration (Table III). A somewhat similar finding was seen with animals receiving griseofulvin in a 100% polyethylene glycol 600 solution dosage form. In animals receiving the solubilized griseofulvin, the controls retained 84% of the dose at 1 hr postdosing while the test animals retained 62%.

As anticipated, propantheline influenced the gastric emptying process by reducing its rate. Even at 11 hr after griseofulvin administration, 36% of the suspension (Table III) and 46% of the solution (Table IV) could be found in the stomach.

Table III also contains the plasma griseofulvin levels at the time of determination of the gastric contents. These plasma levels are in good agreement with those observed in the suspension dosage form plasma level studies (Fig. 1).

The gastric emptying rate in all three groups of rats (controls, metoclopramide pretreated, and propantheline pretreated) was lower when the drug was administered in polyethylene glycol 600 as compared to the suspension (Tables III and IV). However, large intersubject variations and the limited number of experimental data do not permit a definitive evaluation. Griseofulvin administration in polyethylene glycol 600 also caused a noticeable change in the appearance of the gut along with an apparent tendency to retain water.

SUMMARY

The observed plasma level data and gastric emptying experiments suggest that the absorption of the griseofulvin suspension may be limited by two major factors, the gastric emptying rate and the dissolution process. The shorter onset of absorption of the griseofulvin suspension following metoclopramide predosing was probably due to the higher gastric emptying rate, and the lower relative availability was due to the slow dissolution rate when the suspension was forced out of the absorption site prior to complete absorption. On the other hand, propantheline pretreatment resulted in a delayed T_{max}, perhaps due to a very low gastric emptying rate; the undissolved drug traveled through the GI tract very slowly, permitting more drug dissolution and subsequent absorption.

The oral solution studies and gastric emptying experiments support the preceding explanation. With an oral solution of griseofulvin, the drug is readily available and a dissolution process is not involved; the absorption is more rapid and begins from the moment that the dosage form contacts the absorption site. Metoclopramide pretreatment markedly increased the bioavailability of the solution because the transit time in the GI tract was shortened; since there was no dissolution process to delay absorption, the drug was quickly exposed to the proximal small intestine where absorption was rapid.

Finally, propantheline preadministration prior to a solution dosage form of griseofulvin adversely influences the availability of the poorly absorbed antifungal agent through a mechanism not completely understood. Nevertheless, the noted interaction of the motility modifiers with griseofulvin is of particular interest since the results are dependent upon the formulation of griseofulvin administered.

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