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GRISEOFULVIN ABSORPTION FROM DIFFERENT SITES IN THE HUMAN SMALL INTESTINE*

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ABSTRACT

The site-dependent small-intestinal absorption pattern of griseofulvin was investigated in man. Griseofulvin was chosen as a model substance having extremely low water solubility and moderate lipid solubility. A conventional steady-state perfusion technique (triple-lumen tubing system with a 20 cm test segment) was applied. Dissolved griseofulvin ($10 \cdot 0$ mg L^{-1}) was perfused (10 mL min^{-1}) during 160 min into different parts of the small intestine with the middle of the test segment between 85 cm and 270 cm beyond the teeth. Each of the ten healthy volunteers was examined twice with the test segment localized in different regions to allow for intraindividual comparisons. Mean drug absorption rates calculated from intestinal aspirate concentrations were similar in the two intestinal parts (proximal, $15 \cdot 0 \pm 5 \cdot 9$ μg (20 cm min)$^{-1}$; distal, $16 \cdot 2 \pm 4 \cdot 3$ μg (20 cm min)$^{-1}$; mean ± SD). Absorption rate was strongly correlated to the amount of griseofulvin offered to the test segment per unit time. Extrapolating these findings it follows that an amount of griseofulvin, once dissolved, would be absorbed completely (>99%) along 100 cm of the small intestine. A significant, positive correlation between the rate of transmucosal fluid transport and the absorption rate of griseofulvin was observed in the distal parts investigated.

KEY WORDS Small intestine Absorption Griseofulvin Intestinal perfusion Solvent drag

INTRODUCTION

Oral sustained-release formulations generally tend to prolong duration of drug effects by protracting drug release within the gastrointestinal tract, thus spreading the absorption over a greater part of the intestine compared to conventional formulations. Consequently, a drug usually completely absorbed from the proximal parts of the small intestine may be available for absorption throughout the entire small intestine (as well as the large intestine). For sustained-release formulations, efficient drug absorption must not be confined to the upper small intestine, or the prolongation of the effect may be missed and the bioavailability reduced.

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In general, however, the exact extension of the intestinal site(s) with efficient absorption capability as well as the region where absorption might drop are not known, despite the great number of sustained-release formulations introduced.

The drug absorption pattern along the gastrointestinal tract is determined by the interrelationship between physicochemical properties of the drug investigated and the physiological conditions for the permeation process existing within the different parts of the tract.[1] Consequently, a key to study site-dependent drug absorption seems to be the systematic examination of model substances selected according to their different physicochemical natures.

The present investigation was designed to quantitate and compare the absorption parameters of griseofulvin in different parts of the small intestine in man. Griseofulvin was chosen within a series of model drugs[2–5] differing in their physicochemical properties (e.g., pH-dependent octanol: buffer partition coefficient, water solubility, pK, and molecular weight). It is a substance with extremely low water solubility ($4{\cdot}1 \times 10^{-5}$ mol L^{-1}, 37 °C) and a moderate lipid solubility expressed by a partition coefficient of 11 (*n*-octanol:buffer, 37 °C); both of the solubility parameters are only slightly affected by changing pH values within the range occurring in the intestine (pH 6–8).[6]

Griseofulvin absorption after oral administration is well known to be affected by many biopharmaceutical and physiological factors, e.g., the dosage formulation (particle size, dissolution rate, solubility), the presence of surfactants (including bile acids), food, and the dosage regimen (for a review see the article by Schäfer-Korting).[7] Therefore, the method to be employed in the present investigation should allow the comparative quantification of griseofulvin absorption excluding all the processes preceding the drug permeation through the intestinal mucosa. Therefore, the absorption of griseofulvin in man has now been studied by a direct method using an intestinal intubation and perfusion technique.

METHODS

Subjects

Ten healthy volunteers (three females, seven males), between the ages of 24 and 27 years, weighing between 55 and 78 kg with body heights between 164 and 187 cm, were recruited for this open study. None had a history of bowel or cardiovascular disease and the results of liver and renal function tests were normal. Volunteers provided written informed consent prior to entry into the study. The study protocol and subject consent form were approved by the Ethics Committee of the Medical Faculty Dresden.

General procedure

Intestinal steady-state perfusion studies were carried out in the standard fashion utilizing the triple-lumen technique.[8,9] The triple-lumen tubes were

prepared by fusing single polyvinyl tubes (ID 1·0 mm for the perfusion tube and 1·5 mm for aspiration tubes) with tetrahydrofuran. The rubber tip of the tube was filled with 1 mL mercury to facilitate transit. The mixing segment of the tube (distance between the perfusion port and the proximal aspiration port) was 15 cm, and the test segment (distance between the proximal and distal aspiration port) was 20 cm.

Intestinal absorption rates of griseofulvin were determined while perfusing an isotonic saline solution (pH 7·9–8·2, 37 °C) containing (mmol L^{-1}) Na^+ 145, K^+ 5, HCO_3^- 10, Cl^- 140, and polyethylene glycol (PEG) 4000 3 g L^{-1}. PEG was added as a non-absorbable marker to correct the absorption rates of griseofulvin for intestinal fluid movements. Moreover, the PEG concentrations, measured at both aspiration ports were used to calculate the net fluid flow across the intestinal mucosa within the test segment.

In the perfusion solution 10·0 mg L^{-1} ($2·8 \times 10^{-5}$ mol L^{-1}) griseofulvin was dissolved. This concentration was below the maximum water solubility of griseofulvin to prevent its precipitation due to rapid absorption of water from the intestinal segment under study.

The solution was perfused into the intestine at a rate of 10 mL min^{-1} and each perfusion lasted for 160 min. After an equilibration period of 70 min, six successive 15 min samples were collected (by continuous aspiration at 1·5 mL min^{-1}) from proximal and distal aspiration ports (aspirates Nos. P1–P6 and D1–D6, respectively). Sampling at the distal aspiration port was staggered by 15 min to allow for intestinal transit. In this way five calculations (P1D2–P5D6) could be performed for each perfusion study. Steady-state conditions along the test segment were assumed if PEG concentrations remained nearly constant at both aspiration ports during the six sampling periods, i.e. ranging within ±20% of the median PEG concentration.

The colour of intestinal aspirates was registered and sample volume, pH, and the bile acid concentration were measured. Pooled aspirates were subjected to equilibrium dialysis[10] to examine binding of griseofulvin to any macromolecular constituents of the intestinal content.

Calculations and statistics were as follows. Net absorption rates were calculated by standard non-absorbable marker equations[11] (see the article by Gramatté and Richter).[3] The amount of griseofulvin absorbed from the test segment per unit time, i.e. the absorption rate (μg (20 cm $min)^{-1}$), was calculated as the difference between the amount entering and that leaving the test segment. The transport rate of water (mL (20 cm $min)^{-1}$) was determined from the differences between the PEG concentrations in the perfused solution and at the aspiration ports, since equal amounts of this marker entered and left the test segment. A positive rate indicates that water had been absorbed and a negative value that water had been secreted.

The calculated absorption rates of griseofulvin were checked for linear correlation to the perfusion rates of griseofulvin as well as for a correlation to the rates of water movement. The perfusion rate (μg min^{-1}) is the amount

of griseofulvin offered to the test segment per unit time (fluid volume entering the test segment × concentration of griseofulvin in this fluid). In addition, conventional partial and multiple correlation/regression analyses[12] were performed to distinguish the simultaneous influences of the perfusion rate and the water transport on the absorption rate of griseofulvin. The *SPSS for Windows* computer package (version 5·0·1, SPSS Inc., 1992) was used to carry out statistical analyses. Comparisons of mean values were made using the non-parametric Mann–Whitney U test. In general, a p value $<0{\cdot}05$ was considered statistically significant.

Study course

Each of the volunteers was examined twice. On the first study day subjects were intubated by mouth after an overnight fast and the tube was positioned with the middle of the test segment between 85 and 145 cm beyond the teeth. Correct passage of the tube from the stomach into the duodenum was monitored by measurement of pH change in aspirates from each of the three tube openings. Further progress of the tube was followed by consecutive appearance of bile-stained intestinal aspirate. Once the tube had reached the desired distance from the teeth the perfusion was started after tube slacking—if any—had been removed. Small fluid samples were withdrawn from each of the tube channels just before the start of the drug perfusion and their pH and colour were noted to confirm placement and to check for patency of the tube. During the perfusion the subjects were comfortably placed in a semi-supine position and could sleep without restraint. Two hours after finishing the first perfusion study each subject was permitted oral fluids and a low-residue diet, and the tube was allowed to advance distally under the influence of peristalsis.

On the following morning, at least 16 h after beginning the first perfusion, a second perfusion was started when the middle of the test segment was 175–270 cm from the teeth. In this way intrasubject comparisons of proximal with the more distal perfusions could be performed (for individual locations of the tubes see Table 2). After the second perfusion study the tube was removed.

Analytical procedures

Frozen aspirates (1 mL) were thawed and griseofulvin was extracted twice with diethylether (5 and 3 mL) following Garceau *et al.*[13] Combined extracts were evaporated to dryness (38 °C), redissolved in methanol:water (1:1), and measured by spectrofluorimetry with excitation/emission wavelengths of 300/434 nm. For each perfusion study samples of griseofulvin-free intestinal aspirates (obtained before starting the perfusion of griseofulvin-containing solution) were used as individual blanks. They were spiked with solutions of various griseofulvin concentrations, assayed by the described procedure, and compared to absolute standards. Mean recoveries of griseofulvin were >95%.

The analytes were quantitated according to standard curves generated by linear least squares regression analysis ($r > 0.97$; concentration range between 0 and 10 $\mu g\,mL^{-1}$). The lower limit of quantification was 0·1 $\mu g\,mL^{-1}$, with a coefficient of variation of 12% (six separate standard curves).

The amount of PEG in each intestinal sample was determined turbidimetrically.[14] Total bile acid concentrations were measured spectrofluorimetrically.[15]

RESULTS

The procedure described was well tolerated by all volunteers. The tubes moved downward without any problems and no tube slacking occurred. No side effects arose from the direct administration of griseofulvin into the small intestine.

The pH of the intestinal aspirates rose continuously with the distance of the aspiration site from the teeth (an average of pH 6·8 at 85 cm beyond the teeth to pH 7·7 at 270 cm) resulting in a strong, positive correlation between the distance and the pH ($r = 0{\cdot}66$, $p < 0{\cdot}001$, $n = 147$). The mean pH values measured in the aspirates of the middle parts as well as of the most distal regions investigated were higher compared to the proximal mean (Table 1).

There was no binding of griseofulvin to any macromolecular constituents of intestinal fluids as demonstrated by equilibrium dialysis of 10 pooled aspirates.

During four of the 20 perfusions the PEG concentrations at one of the aspiration ports exceeded the range of ±20% of their respective median concentration, indicating that steady-state conditions within the test segment were not established (see Table 2). Altogether, 74 single values of absorption rates could be calculated from the 16 steady-state perfusions.

The concentration of griseofulvin at the entry into the test segment (proximal aspiration port) as well as its perfusion rate (Table 1) were of the same magnitude and range during the proximal and the more distal perfusions performed.

Table 1. Results of griseofulvin perfusion studies performed in different parts of the small intestine (mean ± SD)

Location of the test segment[a] (cm)	Number of perfusions performed	pH value	Rate of water transport (mL (20 cm min)$^{-1}$)	Perfusion rate of griseofulvin ($\mu g\ min^{-1}$)	Absorption rate of griseofulvin (μg (20 cm min)$^{-1}$)
85–110	7	6.80 ± 0.34	1.13 ± 1.32	23.3 ± 8.0	14.6 ± 6.4
125–175	3	7.27 ± 0.27[b]	0.36 ± 1.28[b]	24.7 ± 11.0	16.4 ± 3.4
215–270	6	7.43 ± 0.30[b]	1.00 ± 1.46	22.2 ± 5.2	16.2 ± 4.4

[a]Distance of the middle of the test segment from the teeth.
[b]$p < 0{\cdot}05$ compared to the mean of the proximal values.

Table 2. Intrasubject median values of the perfusion rate, the rate of water transport, and the intestinal absorption rate of griseofulvin in different regions of the small intestine

Subject	Location of the test segment[a] (cm)	Perfusion rate of griseofulvin (μg min^{-1})	Rate of water transport[b] (mL (20 cm min)$^{-1}$)	Absorption rate of griseofulvin (μg (20 cm min)$^{-1}$)
1	85/215	28·6/15·6	1·82/−0·26	16·6/9·8
2[c]	90/170	34·4/—	3·16/—	26·9/—
3	90/175	20·0/19·3	1·11/1·99	13·9/15·3
4[c]	100/200	14·0/—	0·32/—	7·9/—
5	95/240	16·2/18·9	−0·80/3·20	9·4/17·2
6	100/260	26·3/24·7	1·28/−0·10	15·4/17·4
7	110/270	24·7/26·6	0·28/0·17	11·9/13·6
8[c]	125/205	35·8/—	−0·86/—	18·1/—
9	145/240	14·7/23·8	−0·04/1·67	12·8/21·2
10[c]	155/250	—/21·8	—/0·43	—/13·5

[a]Distance of the middle of the test segment from the teeth for the proximal/distal perfusion.
[b]Negative values indicate secretion of water into the test segment.
[c]Steady-state conditions within the test segment were only achieved during one perfusion study.

The mean absorption rates of griseofulvin measured in a 20 cm segment of the small intestine were similar in all regions investigated (Table 1). The mean of all rates measured during the proximal perfusions amounted to $15{\cdot}0 \pm 5{\cdot}9$ μg (20 cm min)$^{-1}$ and the mean of all distal measurements to $16{\cdot}2 \pm 4{\cdot}3$ μg (20 cm min)$^{-1}$ (Figure 1). The absorption rate was linearly related to the perfusion rate (Figure 2); i.e. an increase of the amount of griseofulvin offered to the test segment per unit time caused a corresponding increase of the amount absorbed during the same time. The correlation coefficient of this relationship ($r = 0{\cdot}79$, $n = 74$) was slightly increased to 0·81 by a partial correlation analysis that eliminated the rate of water transport as a potential factor influencing the absorption rate of griseofulvin simultaneously. This strong correlation was also found to be valid after separation of the results according to the different intestinal regions. These regression lines were congruent with nearly identical slopes for the upper and lower perfusions (0·56 against 0·59). In the same way, this relationship could be demonstrated in each intrasubject evaluation: the individual slopes ranged from 0·53 (subject 1) to 0·82 (subject 9) (Figure 3) with coefficients of correlation between 0·74 and 0·99.

The mean rates of water transport were equal in the proximal and distal segments investigated. However, secretion of water was observed frequently (seven out of 12 values were negative) within the mid-regions (test segment 125, 145, and 175 cm beyond the teeth), whereas secretion was found only for four out of 33 and for eight out of 29 measurements in the proximal and distal parts, respectively. Thus a distinctly lower mean rate of water transport was calculated for the middle part of the small intestine (Table 1).

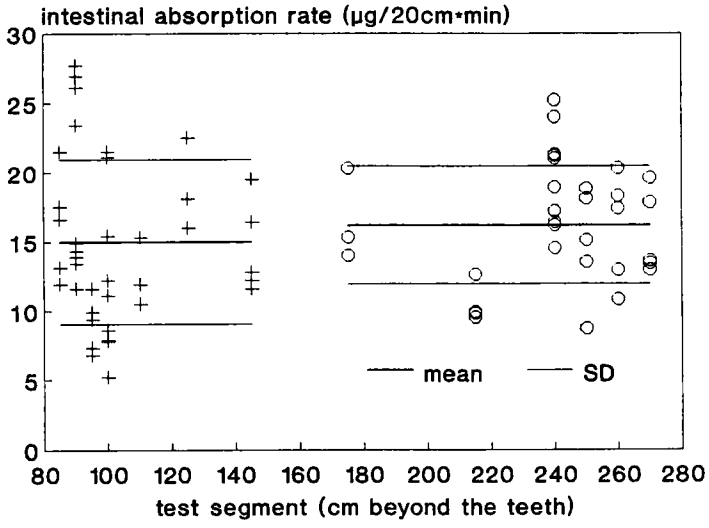

Figure 1. Intestinal absorption rates of griseofulvin in different regions of the small intestine: results of the individual proximal (+) and of the more distal perfusions (○)

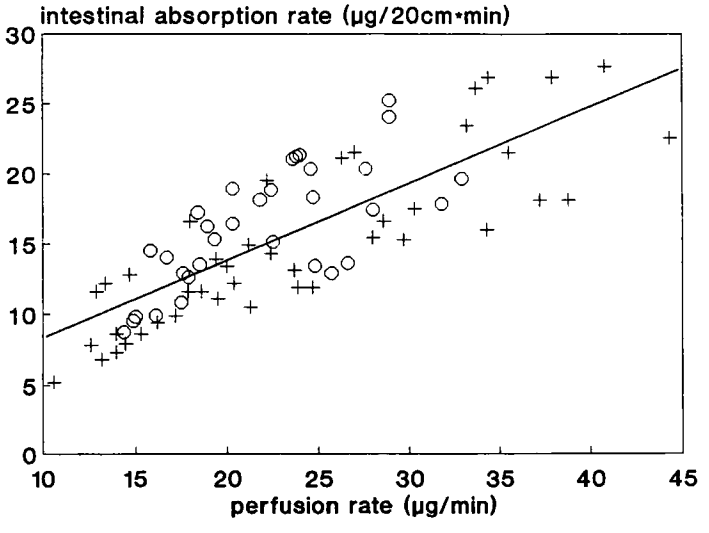

Figure 2. The correlation between the perfusion rate of griseofulvin and its intestinal absorption rate ($r = 0{\cdot}79$, $n = 74$) in the small intestine; proximal results with the test segments between 85 cm and 145 cm beyond the teeth (+); distal results with the test segments between 175 cm and 270 cm beyond the teeth (○)

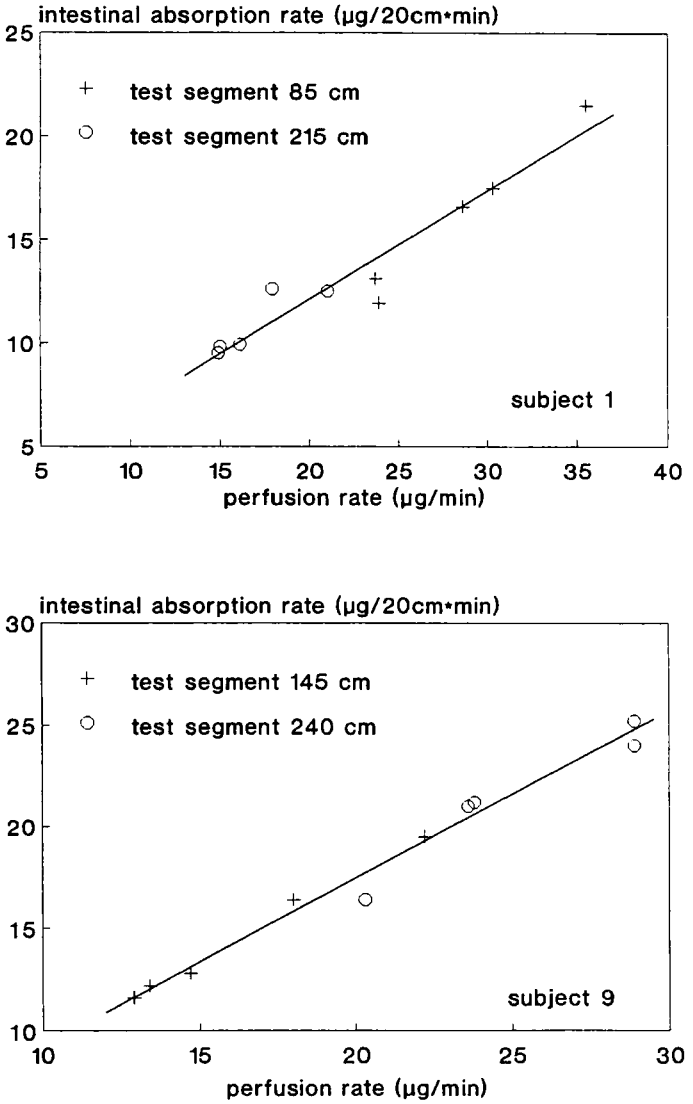

Figure 3. The intraindividual relation between the perfusion rate of griseofulvin and its intestinal absorption rate for the subjects showing the flattest slope (subject 1, slope = 0·53, $r = 0·96$) and the steepest slope (subject 9, slope = 0·82, $r = 0·99$); the location of the middle of the test segments is given in centimetres beyond the teeth

There was a significant positive correlation between the rate of water transport and the absorption rate of griseofulvin in the distal regions investigated. This relation became evident by partial correlation analysis that eliminated the predominant effect of the perfusion rate on the absorption rate (partial correlation coefficient, 0·73, $p < 0·001$). However, multiple-regression analysis,

considering both the perfusion rate and the rate of water transport as variables determining the absorption rate, revealed the effect of water movement to be low. From the multiple-regression equation (absorption rate = 3·5 + 0·5 × perfusion rate + 1·6 × water transport rate; multiple correlation coefficient, 0·87) it follows that the absorption rate is modified by 1·6 μg (20 cm min)$^{-1}$ if the rate of water transport in the distal small intestine changes by 1 mL (20 cm min)$^{-1}$. This modification of the absorption rate corresponds to only 10% of the mean absorption rate measured in this region.

The intrasubject comparisons of the median absorption rates revealed similar results for three of the six volunteers who had been evaluated twice (Table 2). Intraindividual differences of the absorption rates calculated for subjects 1, 5, and 9 may be explained by different perfusion conditions established in the segments under study: the low distal absorption rate of subject 1 (9·8 against 16·6 μg (20 cm min)$^{-1}$) is due to a rather small perfusion rate, which is the lowest observed within all distal studies. This low rate is caused by a low median griseofulvin concentration (1·70 μg mL^{-1}) offered to the test segment. Moreover, this perfusion was accompanied by the lowest median rate of water transport measured in any of the distal studies. The low proximal absorption rate of subject 9 (12·8 against 21·2 μg (20 cm min)$^{-1}$) may be caused by the same factors as mentioned for subject 1 (see Table 2). Accordingly, if there were identical perfusion conditions within the two segments studied individually, similar absorption rates would result in the proximal and distal regions of subject 1 and 9 too. This assumption is emphazised by the common regression line for the relation between perfusion rate and absorption rate, which is appropriate for both the proximal and the distal observations (see Figure 3). The different median absorption rates calculated in subject 5 might be best explained by the extreme difference between the rates of water transport (−0·80 against 3·20 mL (20 cm min)$^{-1}$); the distal rate represents the highest median calculated for any of the perfusions.

In none of the intestinal samples did the concentration of bile acids reach the critical micellar concentration of 4 mmol L^{-1}. There were no correlations between intraluminal bile acid concentration and the intestinal movement of griseofulvin or water.

DISCUSSION

In the present investigation the absorption of griseofulvin was quantitated in different regions of the small intestine in man. Griseofulvin was selected as a model drug because of its very low aqueous solubility and moderate lipid solubility (within the pH range occurring in the human small intestine). The intestinal mucosa is usually highly permeable to such substances, but the overall absorption process may be slow or sometimes even very slow because of limiting solubility in gastrointestinal fluids (as demonstrated, e.g. for griseofulvin and

more recently for the steroid derivative danazol).[16] Incomplete drug availability therefore arises from a different set of circumstances compared to those substances showing diminished absorption rates in lower parts of the small intestine.[4,5]

All preliminary results on griseofulvin absorption and bioavailability have been based either on indirect evaluation by measuring serum drug concentrations or urinary excretion of the main griseofulvin metabolite.[7,17–21] In contrast, the triple-lumen perfusion technique employed here allows a direct measurement of drug disappearance from the intestinal lumen and excludes all factors preceding the permeation through the intestinal mucosa. However, this disappearance may be influenced by factors other than absorption, e.g. intestinal metabolism and binding to intraluminal constituents or intestinal mucosa. However, the results reported indicate griseofulvin disappearance from the test segment to be caused by drug absorption: the absorption rate was shown to be linearly related to the amount of griseofulvin offered to the intestinal segment per unit time (perfusion rate). This was found to be valid for a wide range of griseofulvin loads from about 10 to 45 $\mu g\,min^{-1}$. This is indicative of drug absorption by passive diffusion. There was no binding of griseofulvin to any macromolecular constituents of intestinal fluids as demonstrated by equilibrium dialysis of pooled aspirates; i.e. all griseofulvin perfused into the intestinal lumen was available for absorption. Moreover, the extent of binding to intestinal mucosa (if any) should not vary in the different parts of the small intestine investigated. Also, there is no hint in the literature of any non-hepatic (intestinal) metabolism of griseofulvin.

The intra- as well as interindividual locations of the test segments resulted in a close-meshed mapping of intestinal perfusion sites. The correct passage of the tubes could be followed by monitoring the consecutive appearance of physiological indicators (pH change and bile staining) over each of the three tube openings. In this way the orthograde transport of the tube from the stomach into the small intestine was clearly indicated. No fluoroscopy was performed, because the exact anatomical location of the tube was not of primary interest. It was of decisive importance that the tube was positioned more distally on the second study day compared to the position on the first day. After the first perfusion the tube was left within the intestine and was allowed to move distally under the influence of peristalsis. In this way it was possible to compare the results of two different locations intraindividually. The results concerning the pH measured in the aspirates from different intestinal parts presented further indication for proper position of the tubes according to the results of, e.g., Borgström *et al.* and Evans *et al.*[22,23]

All results clearly indicate that griseofulvin absorption is efficient and uniform throughout the entire length of the small intestinal tract if the dissolved drug is supplied intraluminally. The regression lines of the relationship between griseofulvin perfusion rate and absorption rate were congruent in the upper and lower regions investigated. Moreover, due to the intrasubject similarity of the

slopes of these regression lines it was possible to demonstrate similar intrasubject absorption rates despite the fact that identical perfusion conditions were not established during the two individual perfusions in some subjects. The quite large interindividual range found for the slopes (between 0·53 and 0·82) might be used to explain, at least partly, the intersubject variation reported for griseofulvin pharmacokinetics after oral administration.[17,19]

Relating the absorption rates to the perfusion rates, a mean percentage absorbed of $68 \cdot 1 \pm 14 \cdot 2\%$ $(20\,cm)^{-1}$ may be calculated. Extrapolating these findings it follows that an amount of griseofulvin, once dissolved, would be absorbed completely (>99%) along 100 cm of the small intestine. Consequently, the slow, long-lasting, and sometimes incomplete absorption of griseofulvin, described, e.g., by Rowland *et al.*,[17] could not be caused by a slow intestinal permeation process, but seems to be entirely due to sustained and/or prolonged drug release and dissolution.

Results regarding the rates of small intestinal water absorption as well as secretion were in accordance with data from literature.[24–26] Accordingly, a net secretion of fluid into different parts of the human small intestine is not exceptional.[27,28] There is no explanation, however, for the occurrence of net secretion only within the middle parts investigated. It could not be decided from data within the literature whether this observation might be physiological or coincidental. By using the same study design, similar rates of fluid secretion were observed in the same intestinal region of volunteers investigated regarding the site-dependent small-intestinal absorption of ranitidine.[4]

The study presented is one of the rare reports dealing with drug absorption processes being affected by transmucosal fluid movement in man.[3,4,29,30] There may be a 'solvent-drag' effect influencing the griseofulvin absorption via paracellular aqueous pores or channels ('leaky junctions').[31,32] Although for griseofulvin the efficiency of this convective route was estimated to be low and restricted to the distal part, our findings indicate that this phenomenon seems to exist not only for hydrophilic substances as generally described in animal studies (*in vitro* and *in situ*).[33–37] In man the effective pore radius is about 8 Å in the proximal small intestine and 3 Å in the lower parts.[11,25] However, the incidence of pores is much higher in the distal small intestine. This might be one reason for the fact that a correlation between intestinal fluid movement and the griseofulvin absorption rate could be demonstrated only in the distal parts investigated.

There are only a few results regarding small-intestinal absorption patterns of other drugs suitable for comparing to our findings: similar absorption parameters along the human small intestine were deduced indirectly from similar serum pharmacokinetics as well as directly from similar intestinal absorption rates for metoprolol,[38] sulphamerazine (a sulphonamide),[2] and paracetamol.[3] In contrast, the absorption of the β_1-adrenoceptor antagonist talinolol[5] and of the H_2-antagonist ranitidine[4] were markedly reduced already in the middle parts of the small intestine as could be demonstrated by simultaneous measurements of serum concentrations and intestinal absorption rates.

There are potentially many factors, both physicochemical and physiological, that determine the site-dependent small-intestinal absorption patterns of a drug, and it seems unrealistic to believe that such a complex phenomenon could ever be adequately described by simple physicochemical models (pH partition). Nevertheless, in the context of drug formulation design even minor improvements in the ability to predict such an important component of drug disposition can have major benefits. Results presented demonstrate that there may be a uniform as well as efficient mucosal permeation along the entire small intestine in man, despite the extremely hydrophobic character of the drug considered.

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