Use of 24-hr Urinary Excretion Data to Assess Bioavailability of Griseofulvin in Humans

Keyphrases □ Griseofulvin—bioavailability, use of 24-hr urinary excretion data, humans ■ Bioavailability—assessment using 24-hr urinary excretion data, humans

To the Editor:

Clinical failure with griseofulvin therapy is most probably caused by the slow rate and low extent of absorption and by the appreciable intrasubject and intersubject variations in the bioavailability of this antifungal antibiotic from commercial products (1–3). Accordingly, in 1967, the Department of Health, Education, and Welfare's Task Force on Prescription Drugs recommended to the Food and Drug Administration that bioavailability studies be initiated on griseofulvin products (4). However, to date, bioavailability information only exists for drug products manufactured by the three major producers (5–10). To our knowledge, the literature is devoid of such information for any of the numerous generic products currently on the market. The available data indicate that *only* 50% of an oral dose of micronized griseofulvin is absorbed from the three innovators' products, irrespective of the type of dosage form administered, and that drug absorption is quite variable (5–7, 9).

After administration of a single therapeutic dose (500–1000 mg) of micronized griseofulvin to humans, plasma antibiotic levels are low (peak level of 1–3 μg/ml) and decline to undetectable levels in approximately 72 hr (5, 6, 10). In addition, drug absorption appears to occur over 30–40 hr (5–7, 9, 10). Consequently, one of the best methods for assessing single-dose bioavailability differences in humans among various commerical griseofulvin products is a urinary excretion method in which total 6-desmethylgriseofulvin (free and glucuronide conjugate), the major urinary metabolite, is determined (7–10). This method requires quantitative urine collections for 72–96 hr after drug administration. This relatively long collection period, which is based on an average biological half-life of 11–14 hr (5, 7, 9), increases the chances for a lack of compliance to the experimental protocol on the part of subjects participating in griseofulvin bioavailability studies. This communication describes the results of attempts to determine if the bioavailability of griseofulvin could be adequately assessed from 24-hr, rather than 72- or 96-hr, total 6-desmethylgriseofulvin urinary excretion data.

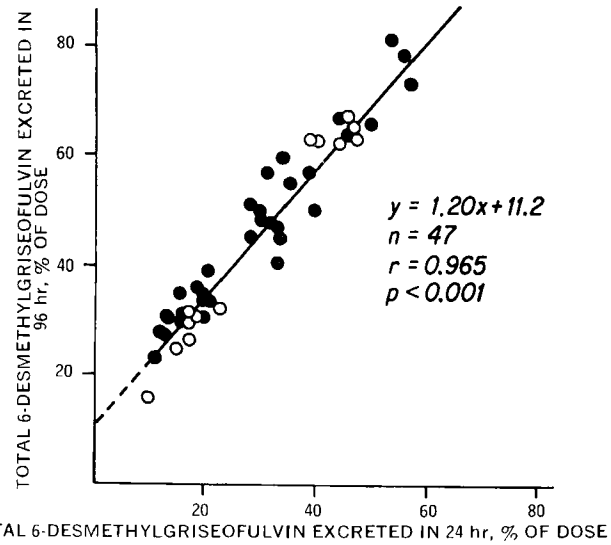


Figure 1—*Relationship between the 96- and 24-hr cumulative amounts of total 6-desmethylgriseofulvin excreted in the urine after administration of a 500-mg oral dose of griseofulvin in various dosage forms to humans. Key:* ●, *data from Refs. 9 and 11; and* ○, *data from Ref. 7.*

Figure 1 shows a plot of 96-hr *versus* 24-hr cumulative urinary major metabolite excretion data obtained after single-dose (500 mg) administration of various griseofulvin dosage forms to human volunteers. The 33 closed circles on this correlation plot represent the results obtained in our bioavailability studies after administration of micronized drug as an aqueous suspension, corn oil-in-water emulsion, and two different commercial tablets[1,2] to five fasting subjects (9) and as capsules of the anhydrous and chloroform solvate forms of the drug to four different subjects (11). The 14 data points denoted by open circles were obtained from a study conducted in two subjects (7) in which the absorption of griseofulvin from experimental tablet and capsule dosage forms of drug–polyethylene glycol 6000 coprecipitates was compared with that from a commercial microcrystalline drug tablet[1].

As indicated by the correlation coefficient and the level of significance (Fig. 1), excellent agreement was found to exist between the 24- and 96-hr cumulative urinary metabolite excretion data. Moreover, the overall variability in excretion was similar at the two collection intervals (*i.e.*, the pooled coefficients of variation were 27.9% at 24 hr and 20.4% at 96 hr). The excretion data obtained by Kabasakalian *et al.* (8) after single-dose administration to one subject of various griseofulvin doses and experimental tablet formulations under several study conditions (33 trials) were excluded from the correlation plot (Fig. 1) solely on the basis that only free 6-desmethylgriseofulvin was recovered from the urine whereas there is substantial evidence that the glucuronide conjugate of this metabolite is also excreted in human urine to an appreciable extent (7, 9–11). The fact that consideration of their findings together with those previously cited (Fig. 1) also resulted in a highly significant correlation[3] ($y = 1.39x + 3.31$, $n = 80$, $r = 0.970$, and $p < 0.001$) suggests that perhaps the composition of urine in the 24–96-hr period is constant. These correlations are encouraging since they provide the basis for possible utilization of 24-hr cumulative total 6-desmethylgriseofulvin excretion data as

[1] Grifulvin V, McNeil Lab.
[2] Fulvicin-U/F, Schering Corp.
[3] The cumulative excretion data of Kabasakalian *et al.* (8) tended to plateau in 72 hr. Estimates of 96-hr excretion values were only approximately 2–5% higher than the reported 72-hr values.

an index of griseofulvin bioavailability in humans. Recently, Greenblatt *et al.* (12) suggested that the single-dose bioavailability of digoxin preparations could be assessed in humans from 1-day, rather than 6-day, urinary excretion data.

(1) R. G. Crounse, *J. Invest. Dermatol.*, **37**, 529(1961).
(2) R. G. Crounse, *Arch. Dermatol.*, **87**, 176(1963).
(3) M. Kraml, J. Dubuc, and D. Dvornik, *ibid.*, **87**, 179(1963).
(4) J. D. Lockhart, *Rev. Can. Biol.*, **32**, 143(1973).
(5) M. Rowland, S. Riegelman, and W. L. Epstein, *J. Pharm. Sci.*, **57**, 984(1968).
(6) S. Riegelman, *Drug Info. Bull.*, **3**, 59(1969).
(7) W. E. Chiou and S. Riegelman, *J. Pharm. Sci.*, **60**, 1376(1971).
(8) P. Kabasakalian, M. Katz, B. Rosenkrantz, and E. Townley, *ibid.*, **59**, 595(1970).
(9) T. R. Bates and J. A. L. Sequeira, *ibid.*, in press.
(10) C.-C. Lin, J. Magat, R. Chang, J. McGlotten, and S. Symchowicz, *J. Pharmacol. Exp. Ther.*, **187**, 415(1973).
(11) T. R. Bates, H.-L. Fung, H. Lee, and A. V. Tembo, *Res. Commun. Chem. Pathol. Pharmacol.*, in press.
(12) D. J. Greenblatt, D. W. Duhme, J. Koch-Weser, and T. W. Smith, *Clin. Pharmacol. Ther.*, **16**, 813(1974).

Theodore R. Bates ˣ
Joel A. L. Sequeira

Department of Pharmaceutics
School of Pharmacy
State University of New York at Buffalo
Buffalo, NY 14214

Received December 26, 1974.
Accepted for publication February 5, 1975.
Supported in part by a Merck Grant for Faculty Development from the Merck Company Foundation and by General Research Support Grant FR5-501RR-05454-10 from the General Research Support Branch, Division of Research Facilities and Resources, National Institutes of Health, Bethesda, MD 20014

ˣ To whom inquiries should be directed.

Epicillin and Ampicillin: Crystalline Modifications and Their Physicochemical Differences

Keyphrases □ Epicillin—crystalline modifications, physicochemical properties □ Ampicillin—crystalline modifications, physicochemical properties □ Antibiotics—epicillin and ampicillin, crystalline modifications and their physicochemical differences

To the Editor:

Epicillin (I), a new broad spectrum semisynthetic penicillin, is formed by the coupling of 6-aminopenicillanic acid with D-α-amino-1,4-cyclohexadiene-1-acetic acid (1). Its bacteriology (2, 3), pharmacology, and clinical applications have been reported (4–8). Epicillin is similar to ampicillin (II) in antimicrobial activity, although epicillin may exert a significantly greater bactericidal activity *in vitro* against certain Gram-negative bacteria than does ampicillin (2).

Although the molecular structure of epicillin differs only slightly from that of ampicillin, the difference being confined to the side chain, some physicochemical properties of epicillin differ significantly from those of ampicillin; these differences are reported herein.

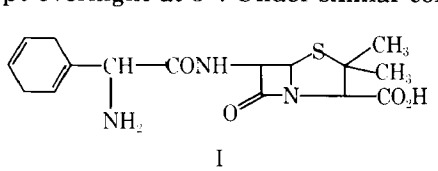
Table I—X-Ray Powder Diffraction Patterns of Epicillin Anhydrate and Epicillin Trihydrate

Epicillin Anhydrate		Epicillin Trihydrate	
d^a	$I/I_1{}^b$	d	I/I_1
11.3	0.17	11.8	0.21
10.7	0.49	8.0	0.11
10.2	0.09	7.8	0.14
6.55	0.06	7.2	0.88
6.15	0.25	5.82	1.00
5.92	0.16	5.44	0.21
5.62	0.22	5.13	0.25
5.48	0.80	5.07	0.21
5.10	0.28	4.90	0.89
4.57	0.04	4.56	0.56
4.41	0.24	4.47	0.28
4.32	0.11	4.40	0.24
4.22	0.20	4.10	0.36
4.11	0.45	4.01	0.41
3.95	0.62	3.95	0.21
3.85	1.00	3.82	0.50
3.75	0.12	3.76	0.59
3.51	0.14	3.60	0.17
3.45	0.12	3.48	0.32
3.40	0.24	3.45	0.52
3.35	0.12	3.32	0.61
3.13	0.01	3.21	0.19
3.07	0.38	3.17	0.15
2.96	0.12	3.08	0.62
2.90	0.12	3.03	0.29
2.85	0.09	2.97	0.24
2.81	0.12	2.91	0.14
2.76	0.11	2.80	0.34
2.69	0.11	2.74	0.18
2.62	0.21	2.69	0.18
2.58	0.12	2.66	0.16
2.48	0.11	2.60	0.21
2.41	0.05	2.58	0.25
2.30	0.11	2.51	0.20
2.25	0.19	2.26	0.23

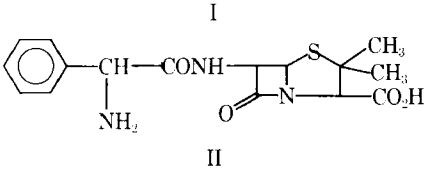
[a] Interplanar spacing in angstrom unit. [b] Relative intensity visual estimation, radiation; Cu/Ni (Norelco, model IC 2000, Philips Electronic Instruments, Mount Vernon, N.Y.).

At room temperature (25°), epicillin trihydrate is about four times more soluble in water than is the anhydrate, 17.8 and 4.1 mg/ml, respectively. In contrast, ampicillin trihydrate is less soluble than is the anhydrate (9, 10), 7 and 10 mg/ml, respectively. In a study of ampicillin solubility at different temperatures, the solubility curves for the anhydrous and trihydrate forms intersected at about 50°, the transition temperature of these two crystalline forms (11); in a similar study, the transition temperature was 42° (10). No clearcut transition temperature is obtainable for the epicillin anhydrate–epicillin trihydrate system.

There is no evidence that epicillin anhydrate is converted to the trihydrate in an acidic slurry, even when kept overnight at 5°. Under similar conditions,



I



II