Dose Adjustment in Renal Failure

Keyphrases □ Renal failure—problems of dose adjustment, rate constants □ Dosage regimens—dose adjustment in renal failure □ Pharmacokinetics—dose adjustment in renal failure, rate constants

To the Editor:

In 1972, Gibaldi and Perrier (1) discussed the problems associated with dose adjustment in patients with renal insufficiency for drugs that obey two-compartment model kinetics. These authors suggested that, due to the curvilinear relationship between the hybrid rate constant β and the elimination rate constant k_{el}, assumption of a linear relationship between endogenous creatinine clearance (C_{cr}) and β may result in underestimation of β, leading to undermedication in some circumstances. They pointed out, however, that due to normal scatter generally observed in clinical data, the assumption of a linear relationship between ln $2/t_{1/2}$ and C_{cr} is still valid for practical purposes.

Added support for the latter comment may be found if one considers the relative magnitude of the distribution and elimination rate constants appropriate to the two-compartment model along with the constraints imposed on β and the associated biological half-life by the values of k_{21} and k_{el}. If one assumes that k_{el} is linearly related to C_{cr} but that k_{12} and k_{21} are invariant, then, as indicated by Gibaldi and Perrier (1), β will approach zero as k_{el} approaches zero but will approach k_{21} as k_{el} increases to large values.

To examine the relationship between curve nonlinearity and rate constant values, curves were constructed based on the parameter values given in Table I.

Plots of β *versus* k_{el} are given in Fig. 1. In each case, the plot is essentially linear at low values of β and k_{el}. When β values fall within this low range, one observes a linear relationship between β and C_{cr}. As the value of k_{el} increases, β approaches k_{21}. The maximum values for β in the four cases are 1.5, 0.1, 1.0, and 0.15 hr^{-1}, equivalent to biological half-lives of 0.46, 6.93, 0.69, and 4.62 hr, respectively.

From Fig. 1, the appropriate β/k_{el} relationships are essentially linear for values of β less than 0.5, 0.03, 0.7, and 0.1 hr^{-1}, equivalent to biological half-lives greater than 1.4, 23.1, 1.0, and 6.9 hr, respectively. In these four cases, a pseudolinear relationship is obtained between β and k_{el}, and hence β and C_{cr}, after

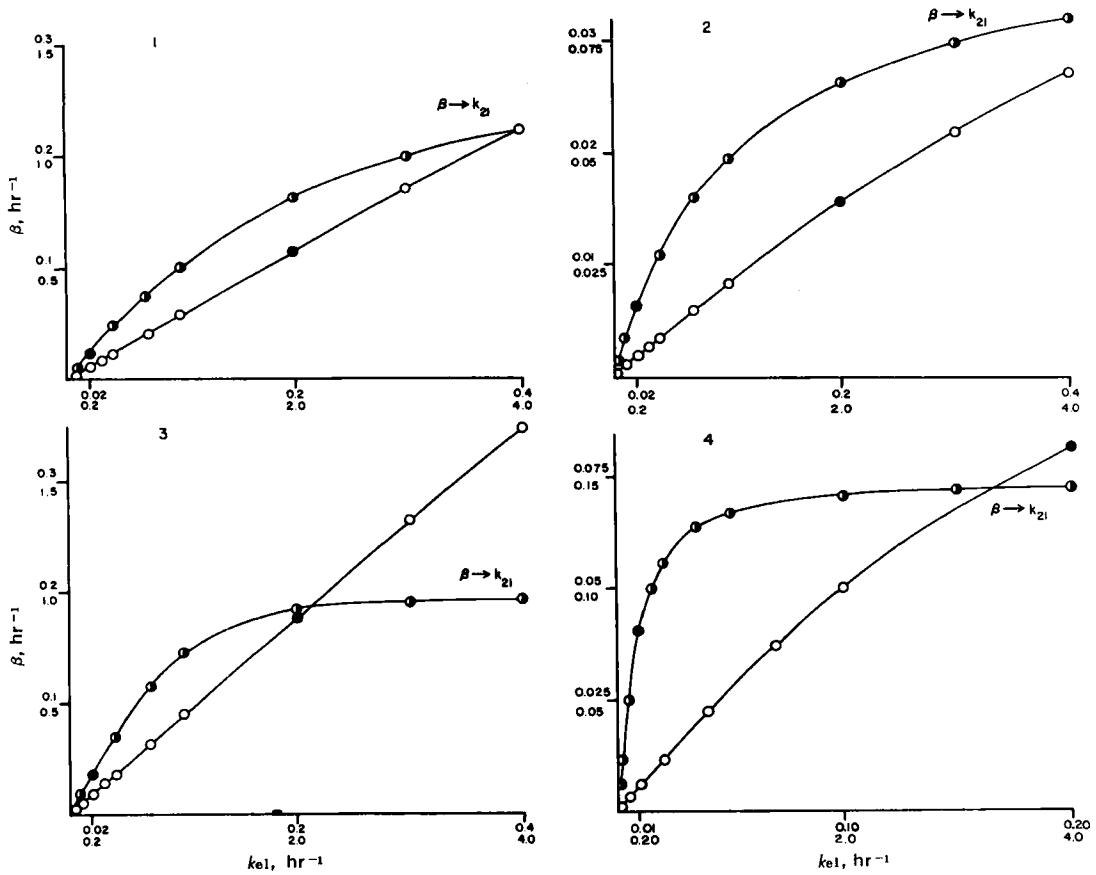

Figure 1—*Relationships between* β *and* k_{el} *in the four situations described in Table I. Key:* ◑, *bottom scale;* ○, *top scale; and* ●, *common point on both scales.*

Table I—Distribution and Elimination Rate Constants

Case	k_{12}	k_{21}	k_{el}
1	1.0	1.5	0.01 → 4.0
2	1.0	0.1	0.01 → 4.0
3	0.1	1.0	0.01 → 4.0
4	0.1	0.15	0.01 → 4.0

half-lives are increased between 1.4 and 3.3 times the minimum possible value. For most drugs, however, biological half-lives in conditions of normal renal function may be considerably longer than the minimum value and a linear relationship might be expected after a much smaller increase in half-life.

Even when the extreme case applies, it is evident from these data that dose adjustment assuming a linear relationship between ln $2/t_{1/2}$ and C_{cr} is a realistic procedure regardless of the pharmacokinetic model. The errors in the assumption would be greatest in conditions of relatively mild renal insufficiency, where dose adjustment might not be considered necessary.

(1) M. Gibaldi and D. Perrier, *J. Pharm. Sci.*, **61**, 952(1972).

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Free Amino Acids in Higher Marine Fungi

Keyphrases □ Marine fungi (higher)—determination of free amino acids from Ascomycetes and Fungi Imperfecti □ Fungi, marine—determination of free amino acids □ Amino acids, free—content of Ascomycetes and Fungi Imperfecti determined

To the Editor:

Attention has been directed to the potential importance of higher marine fungi as contributors of metabolites to marine ecosystems and producers of bioactive compounds (1). Continuing our investigations on the overall metabolic capabilities of these organisms, we now report on the free amino acids of selected marine Ascomycetes and Fungi Imperfecti. Related published reports are limited to that by Schafer and Lane (2), who identified 12 amino acids from hydrolyzed peptides of the Ascomycete *Lulworthia floridana* Meyers, and Kirk's (3) cytochemical investigations of marine pyrenomycete ascospores.

Shake cultures of 10 isolates (Table I) were grown on a yeast extract–glucose–inorganic salts[1] medium and harvested after 7 days as described previously (4). Mycelia were washed thoroughly in cold water,

[1] Rila Marine Mix, Rila Products, Teaneck, N.J.

Table I—Organisms Investigated

Ascomycetes	Isolate[a]
Lignincola laevis Höhnk	R-2
Nais inornata Kohlm.	R-4
Leptosphaeria oraemaris Linder	R-13
Corollospora maritima Werdermann	R-19
Halosphaeria mediosetigera Cribb *et* Cribb	R-524
Halosphaeria hamata (Höhnk) Kohlm.	R-577
Haligena elaterophora Kohlm.	R-601
Halosphaeria appendiculata Linder	R-605
Fungi Imperfecti	
Culcitalna achraspora Meyers *et* Moore	F-1
Zalerion maritimum (Linder) Anastasiou	R-6

[a] Refers to isolate number of particular species as cataloged in the mycological collection of P. W. Kirk, Jr., Old Dominion University, Norfolk, VA 23508

dried in forced air at 40° for 48 hr, and defatted with petroleum ether (bp 30–60°) for 12 hr in a soxhlet apparatus. Extracts of free amino acids were then prepared according to the method of Heathcote *et al.* (5), modified by extending the aqueous extraction phase to 48 hr. These extracts were desalted and purified according to Pocklington (6). The extracts, free from interfering ions and peptides, were analyzed by TLC and GLC.

Aqueous extracts were spotted on thin-layer cellulose plates and developed in a two-dimensional system: isopropanol–butanone–1 *N* HCl (12:3:5) in the first direction and butanol–acetic acid–water (2:1:1) in the second. Identification of the amino acids was achieved by comparing chromatograms of reference amino acids with those of extracts and mixtures of the two. The amino acid spots were revealed by heating plates sprayed with ninhydrin solution.

GLC analyses were based on the method described by Zumwalt *et al.* (7). The instrument[2] used was equipped with a flame-ionization detector. Instrument conditions included: silanized[3] borosilicate glass column, 1.8-m × 0.3-cm (6-ft × 0.125-in.) o.d., packed with 3% methyl silicone on calcined diatomaceous earth[4]; carrier gas, nitrogen at 45 ml/min; oven, 75° increased by 7.5°/min to 300°; detector, 250°; flash heater, 200°.

Reference trimethylsilyl amino acid derivatives were prepared as follows (8). One milligram of amino acid was dissolved in 50 ml of methanol. One milliliter of this stock solution was placed in a 0.6 × 5.1-cm (0.25 × 2-in.) screw-capped vial containing 1 ml of anhydrous methylene chloride. This was heated to 70° in a sand bath to remove the solvent and azeotropically remove all moisture. While the vial remained in the sand bath, its contents were further dried under a stream of nitrogen for 30 min.

To the dried residue was added 0.25 ml of bis(trimethylsilyl)trifluoroacetamide, and this mixture was heated for 1 hr in a sand bath at 135°. After refluxing, the vial was allowed to cool spontaneously. Derivatives of the dried free amino acid extracts were prepared in an identical manner. Freshly prepared

[2] Hewlett-Packard model 402.
[3] Sylon, Supelco, Inc.
[4] 3% OV-1 on Gas Chrom Q, Applied Sciences Labs., Inc.