Equations for Estimation of First-Pass Effect and Apparent Distribution Volume of Drug with Incomplete Oral Absorption and Partial Renal Excretion

Keyphrases □ First-pass effect—estimation and distribution volume, drugs with incomplete oral absorption and partial renal excretion □ Distribution volume—estimation and first-pass effect, drugs with incomplete oral absorption and partial renal excretion □ Absorption, GI, incomplete—estimation of first-pass effect and distribution volume □ Excretion, renal, partial—estimation of first-pass effect and distribution volume

To the Editor:

Equations assuming complete absorption have been used to estimate the degree of pulmonary (1) and hepatic (2, 3) first-pass effect and the apparent distribution volume (1, 3) after oral dosing of drugs having partial pulmonary and renal excretion. The purpose of this communication is to present general equations that can be used when a drug is known to be absorbed only partially from the dosage form.

Based on the previously derived equations (1), the extent of the first-pass effect or the hepatic extraction ratio, designated as f_m, is:

$$f_m = \frac{(F_m)(F)(\text{dose})}{(F)(\text{dose}) + (HFR)(AUC_\infty)} \qquad \text{(Eq. 1)}$$

where F_m is the hepatically metabolized drug fraction after intravenous administration or after entry into the general circulation through other routes of administration, F is the dose fraction available for GI absorption from the dosage form, HFR is the hepatic blood flow rate, and AUC_∞ is the total area under the blood concentration *versus* time curve at infinite time.

The apparent volume of distribution, V_d, based on the area method can be estimated by:

$$V_d = \frac{(F)(1 - f_m)(\text{dose})}{(K_t)(AUC_\infty)} \qquad \text{(Eq. 2)}$$

where K_t is the first-order rate constant of the terminal postabsorption and postdistribution phase.

Similar equations can be derived for drugs that are partially absorbed and partially excreted from the lung and kidney.

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N-Benzoyl Derivatives of Amino Acids and Amino Acid Analogs as Inhibitors in Microbial Antitumor Screen

Keyphrases □ Antineoplastic agents, potential—amino acids, *N*-benzoyl derivatives, microbial screen □ Amino acids, *N*-benzoyl derivatives—potential antineoplastic agents, microbial screen

To the Editor:

For some time, we have been studying the *N*-acylated derivatives of amino acids and amino acid analogs as possible antitumor agents (1–3). Certain chloroacetylated (1, 3) and trifluoroacetylated (4) amino acids and amino acid analogs were found to be active inhibitors of the growth of a microbial system selected for antitumor screening. The degree of inhibition ranged from about 20 to 50%.

With the hope of increasing the activity of these compounds by giving them more lipophilic character, the benzoyl and ring-substituted benzoyl derivatives were prepared. The acylation was accomplished by the conventional Schotten–Baumann procedure (5). The purity of these compounds was ascertained by elemental analysis, melting-point determination, optical rotation determination where applicable, and Van Slyke nitrous acid determination of the primary amino nitrogen (6). The microbiological assay system utilized was *Lactobacillus casei* (7469) in a riboflavin-supplemented riboflavin assay system (3).

Mercaptopurine, a known and accepted antitumor agent, assayed concurrently with the test compounds, showed an inhibition of about 54% at a final concentration of 0.1 mg (0.6 μmole)/ml in this test system. Growth was determined turbidimetrically (3). Initially, the activity was determined at 1 mg/ml, in accord with the screening protocol (7), and the nine most active compounds were compared on an equimolar basis at 4.47 μmoles/ml, the final concentration. This concentration is equivalent to 1 mg of chloroacetyl-β-hydroxy-D-norleucine B/ml, the compound previously found to be the most active in these studies (2).

Of the 28 benzoyl compounds tested, the nine listed in Table I showed pronounced activity, greater than that

Table I—Effect of Equimolar Concentrations of *N*-Benzoyl Derivatives of Amino Acids and Amino Acid Analogs on the Growth of *L. casei* 7469 [a]

Compound	Inhibition[b], %
N-Benzoyl-*o*-fluoro-DL-phenylalanine	82
N-Benzoyl-*m*-fluoro-DL-phenylalanine	96
N-Benzoyl-*p*-fluoro-DL-phenylalanine	72
N-Benzoyl-β-2-thienyl-DL-alanine	76
N-Benzoyl-β-3-thienyl-DL-alanine	56
N^{α}-Benzoyl-L-tryptophan	74
N-Benzoyl-*p*-chloro-DL-phenylalanine	94
N^{α}-Benzoyl-*p*-nitro-L-phenylalanine	78
N^{α}-*p*-Nitrobenzoyl-L-phenylalanine	78

[a] Maximum growth in inoculated control tubes containing no test compound, measured turbidimetrically, was 166-173 Klett units. [b] Concentration was 4.47 μmoles/ml and was the final concentration in the assay system.

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