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Absolute Drug Bioavailability: Approximation without Comparison to Parenteral Dose for Compounds Exhibiting Perturbable Renal Clearance

Keyphrases □ Bioavailability—approximation of absolute drug bioavailability without comparison to parenteral dose for compounds exhibiting a perturbable renal clearance □ Drug bioavailability—approximation without comparison to parenteral dose, compounds exhibiting perturbable renal clearance

To the Editor:

It is generally accepted that the absolute bioavailability of a drug dosage form can only be determined by comparison with a parenteral dose. However, ethical and legal considerations prevent injection of many compounds, greatly inhibiting the acquisition of bioavailability data for new drugs.

The principal purpose of this communication is to demonstrate that it is possible to approximate the absolute bioavailability of a large class of drugs (1), those whose renal clearance is perturbable, without the administration of a parenteral dose. As an example, consider an agent that exhibits an area under the plasma concentration–time curve of AUC under condition X (*e.g.*, coadministration of a urinary acidifying agent) and of AUC' under condition Y (*e.g.*, coadministration of urinary alkalinizing agent). Similarly, let Cl_B, Cl_R, and Cl_{NR} equal the total body clearance, mean renal clearance, and nonrenal clearance, respectively, during condition X, and let the prime notation indicate their values under condition Y. Finally, let D equal the dose administered and F equal the fraction of the dose that is absorbed. The following analysis assumes that: (*a*) the system is linear, and (*b*) Cl_{NR}, F, and intercompartment transfer constants (if any) are independent of the perturbation of renal clearance.

Since:

$$Cl_B = Cl_R + Cl_{NR} \qquad \text{(Eq. 1)}$$

and:

$$Cl_B' = Cl_R' + Cl_{NR} \qquad \text{(Eq. 2)}$$

by letting:

$$Cl_R - Cl_R' = \Delta Cl_R \qquad \text{(Eq. 3)}$$

and:

$$Cl_B - Cl_B' = \Delta Cl_B \qquad \text{(Eq. 4)}$$

it follows that:

$$\Delta Cl_R = \Delta Cl_B = Cl_B - Cl_B' \qquad \text{(Eq. 5)}$$

From the model independent equation:

$$\text{total body clearance} = \frac{DF}{\text{area under the plasma concentration-time curve}} \qquad \text{(Eq. 6)}$$

and Eq. 5, it is apparent that:

$$\Delta Cl_R = \frac{DF}{AUC} - \frac{DF}{AUC'} \qquad \text{(Eq. 7)}$$

or:

$$F = \frac{\Delta Cl_R}{D}\left[\frac{(AUC)\ (AUC')}{AUC' - AUC}\right] \qquad \text{(Eq. 8)}$$

Since all terms on the right-hand side of Eq. 8 can be determined experimentally without reference to a parenteral dose, it follows that absolute bioavailability may be approximated by this method given the validity of the listed assumptions.

(1) A. M. Asatoor, D. R. London, M. D. Milne, and M. L. Simenoff, *Brit. J. Pharmacol.*, **20**, 285(1963).

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Gastric Irritation and Bleeding after Drug Administration

Keyphrases □ Gastric irritation and bleeding—effects of aspirin, phenylbutazone, methyl salicylate, salicylic acid, and triamcinolone, powder and solution forms, effects of polyethylene glycol bases, rats □ Bleeding, gastric—effects of various drugs under varying experimental conditions, rats □ Drug administration—extent of gastric irritation and bleeding caused by aspirin, phenylbutazone, methyl salicylate, salicylic acid, and triamcinolone, powder and solution forms, effects of polyethylene glycol bases, rats

To the Editor:

Many drugs are known to be irritating to the stomach and GI tract, and some have been shown to produce gastric ulceration and bleeding (1–3). This communication describes results obtained in a study to determine if various drugs would induce bleeding or ulceration in the stomach of rats under various experimental conditions.

Seventy rats, 130–150 g, were divided into groups (four to six rats in each group). The rats were fasted in screen-bottom cages for 24 hr prior to drug administration. During the fast, water was allowed *ad libitum*. The animals then received the following drugs