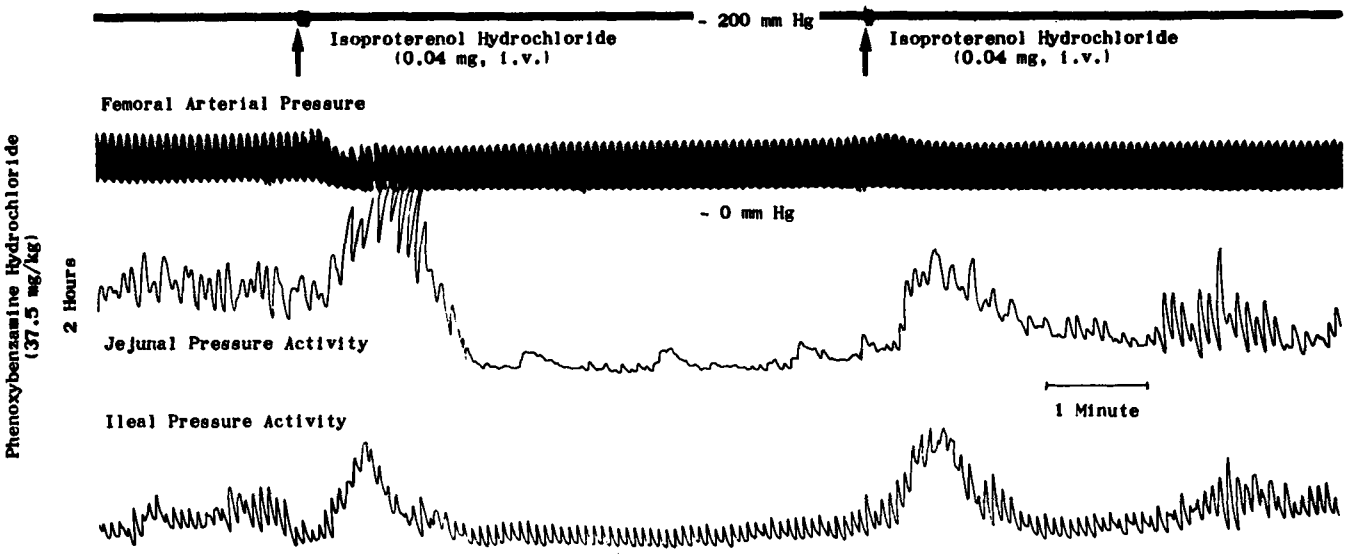

Figure 1—*Polygram showing the effect of intravenous isoproterenol, repeated once, on a phenoxybenzamine background on femoral arterial blood pressure and jejunal and ileal intraluminal pressure activities.*

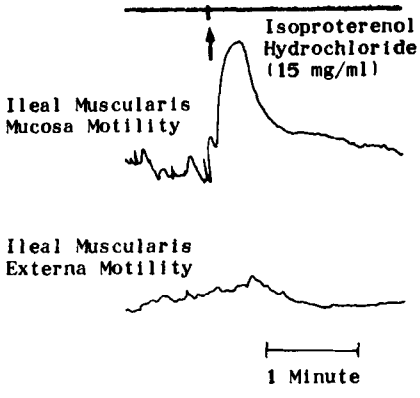

Figure 2—*Polygram showing* in vitro *effects of isoproterenol on the muscular components of the canine ileum.*

A systematic review of the literature indicates that, insofar as gross organ motility is concerned, the canine ileum is the one system observed *in vitro* or *in situ* in which the adrenergic effect is not always inhibitory. Basic histology also tells us that this is the only system that exists in the aforementioned species, from the cardia to the rectum, in which the muscularis mucosa forms a physically significant effector layer (similar to humans) in terms of the ratio of layer thickness to inner layer radius.

Therefore, we advance the general proposition that β-adrenergic agents in high doses are usually stimulatory to the muscularis mucosa and that they are potentiated by α-adrenolytics. We also support the proposition that the β-agents are inhibitory of the motility of the tunica muscularis. In terms of gross organ motility, we believe that the net effect of any agent will be primarily determined by its effect on the more physically significant of the coupled effector systems.

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Bioavailability under Variable Renal Clearance Conditions

Keyphrases □ Bioavailability—method for assessment under variable renal clearance conditions □ Renal clearance conditions, variable—effect on bioavailability □ Pharmacokinetics—bioavailability under variable renal clearance conditions

To the Editor:

Several methods are used to calculate the bioavailability of a drug, *i.e.*, the fraction of the administered dose that reaches the general circulation. Bioavailability can be determined from single (1–4) or multiple (5) doses, as well as at steady state (6).

The most popular methods for assessing bioavailability involve single test and reference doses. A comparison determination of the total area under the plasma concentration *versus* time curve, AUC_0^∞, or the total amount excreted unchanged in urine from time = 0 to time = ∞, A_R^∞, between the test dose and a reference dose is made. The assumptions in these methods are:

1. Total plasma clearance is the same in the test dose and reference studies when the areas are used for bioavailability assessment.
2. The fraction excreted unchanged in the urine, f_e, is

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the same in the reference and test studies when the total amount excreted unchanged in the urine is used for determination of bioavailability.

A number of drugs, however, demonstrate urine pH and urine flow dependent renal clearance; unless the experimental conditions are rigidly controlled by acidifying or alkalinizing the urine pH with ammonium chloride or sodium bicarbonate while maintaining constant fluid intake, renal plasma clearance, Cl_R, is likely to vary between and within test and reference studies.

Kwan and Till (7) suggested a method to circumvent this situation. When renal plasma clearance differs between studies, the renal plasma clearance can be determined from the renal excretion rates and the plasma concentrations of the unchanged drug between the experiments. The assumptions in this method are that renal clearance is constant within an experiment (but, of course, can vary between studies) and that the extrarenal plasma clearance is the same between studies.

The assumption of constant renal plasma clearance throughout the individual studies is, at best, an approximation. When studies have to be carried out over longer periods, the renal clearance may vary due to fluctuations in urine flow and urine pH throughout the day, providing the renal clearance is urine pH and urine flow dependent.

We propose a method for the determination of bioavailability that does not require constant renal clearance, neither between experiments nor within an experiment. This method allows for the determination of the bioavailability of a drug without rigid control of urine pH or urine flow, provided the extrarenal plasma clearance is unaltered.

The elimination rate, dA_e/dt, can be described by:

$$\frac{dA_e}{dt} = \frac{dA_{xr}}{dt} + \frac{dA_r}{dt} \qquad \text{(Eq. 1)}$$

where dA_{xr}/dt is the rate of extrarenal elimination and dA_r/dt is the rate of renal excretion.

The extrarenal elimination can be expressed by:

$$\frac{dA_{xr}}{dt} = (Cl_{xr})(C_p) \qquad \text{(Eq. 2)}$$

where Cl_{xr} is the extrarenal clearance and C_p is the plasma concentration.

Substitution of Eq. 2 in Eq. 1 and rearrangement give:

$$dA_e = (Cl_{xr})(C_p)(dt) + dA_r \qquad \text{(Eq. 3)}$$

The total amount eliminated from the body from time = 0 to time = ∞ must be equal to the total amount entering the general circulation, *FD, and* the total amount excreted in the urine from time = 0 to time = ∞ must be equal to the total amount recovered in the urine, A_R^∞.

Therefore, integrating Eq. 3 from time = 0 to time = ∞ gives:

$$FD = \int_0^\infty (Cl_{xr})(C_p)(dt) + A_R^\infty \qquad \text{(Eq. 4)}$$

where F is the bioavailability of the dosage form and D is the amount of drug administered.

Since $\int_0^\infty (C_p)(dt) = AUC_0^\infty$ and Cl_{xr} is assumed to be a constant, the following relationship is obtained:

$$FD = (Cl_{xr})(AUC_0^\infty) + A_R^\infty \qquad \text{(Eq. 5)}$$

When the bioavailability of the reference dose is F^s and the bioavailability of the test dosage form is F^T, F^T can simply be determined by:

$$F^T = \frac{(F^sD^s - A_R^{\infty s})\dfrac{AUC_0^{\infty T}}{AUC_0^{\infty s}} + A_R^{\infty T}}{D^T} \qquad \text{(Eq. 6)}$$

When the reference dose is an intravenous bolus dose where the bioavailability is equal to 1, Eq. 6 can be expressed by:

$$F^T = \frac{(D^s - A_R^{\infty s})\dfrac{AUC_0^{\infty T}}{AUC_0^{\infty s}} + A_R^{\infty T}}{D^T} \qquad \text{(Eq. 7)}$$

To use this method, the total area under the plasma concentration *versus* time curve and the amount excreted unchanged in the urine from time = 0 to time = ∞ for both the test drug and the standard are needed. Except for the assumption of extrarenal plasma clearance constancy, this method does not require a constant renal clearance and fraction excreted unchanged nor an assessment of the pharmacokinetic model. From Eq. 6, it can be seen that this method cannot be used to assess the relative bioavailability of a drug, F^T/F^s, and is only useful when the reference dosage form is an intravenous bolus or if the bioavailability of the reference dose is known.

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Novel Method for Determining Protein Binding of Theophylline

Keyphrases □ Theophylline—protein binding determined by ultrafiltration method □ Protein binding—theophylline, determined by ultrafiltration method □ Binding, protein—theophylline, determined by ultrafiltration method □ Ultrafiltration method—determination of theophylline protein binding □ Relaxants, smooth muscle—theophylline, protein binding determined by ultrafiltration method

To the Editor:

The kinetics of drug elimination and the apparent biological half-life of a drug may be influenced by drug–protein interactions (1). Although interpatient and intrapatient variations in theophylline clearance rates are gen-

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