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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.

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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

by means of an oral stomach tube: 0.5 ml of a solution of aspirin (100 mg/ml) in polyethylene glycol 400, 0.5 ml of a solution of salicylic acid (100 mg/ml) in polyethylene glycol 400, 0.5 ml of 95% alcohol, 0.5 ml of methyl salicylate, 0.5 ml of acetylated and methoxypolyethylene glycol 350, 0.5 ml of a solution of phenylbutazone (20 mg/ml) in polyethylene glycol 400, and 0.5 ml of a solution of caffeine (20 mg/ml) in water. One group of rats received the solution of aspirin in polyethylene glycol rectally.

Drugs were also administered directly into the stomach in powder form; a device for such administration of powder was made in this laboratory. It consisted of a 20-gauge, flexible, hollow stainless steel cannula (about 10 cm) with a piece of tubing fitted to the end. Tubing dimensions were 3.2 mm o.d., 2.4 mm i.d., and 15 mm length. Prior to the drug administration, paraffin oil was applied to the surface of tubing. The tubing was packed with the drugs in powder form, and the powder was forced out into the stomach by depressing the plunger connected to the flexible cannula. Drugs administered in this manner were triamcinolone, phenylbutazone, and aspirin. To study the effect of food in the stomach on the gastric bleeding, one group of rats was allowed food at least 1 hr before the administration of aspirin powder and aspirin solution.

One hour after administration of the various drugs, each group of rats was sacrificed with chloroform. The stomach was removed, opened along the line of lesser curvature, and observed for the presence of bleeding or ulceration.

In the rats that received the aspirin solution orally, an average of four or five lesions and some slight bleeding were observed. There was evidence of ulceration and bleeding in the rats that received 25 mg of aspirin in powder form. The rats that received the solution of salicylic acid had a large amount of bleeding, and gastric lesions were produced.

The alcohol produced a large extent of irritation and erythema of the stomach mucosa but no bleeding or lesions. This result is in contrast to the finding of Morris *et al.* (4), who reported that the administration of 0.3 ml of 30% ethanol solution orally produced gastric lesions in the stomach of the rat. The number and severity of the lesions were similar to those produced by the administration of aspirin solution.

Rats that received acetylated and methoxypolyethylene glycol base showed no bleeding or lesion production, with the exception of one rat in the group. There was extensive dilatation of the blood vessels of the stomach of one rat following administration of acetylated polyethylene glycol base. The substituted polyethylene glycol 400 was used to see whether chemical alteration of the base has any effect on gastric irritation. The administration of methyl salicylate produced some slight redness and irritation of the stomach mucosa, but no bleeding or ulceration was observed.

The administration of phenylbutazone in a solution produced four or five lesions in the stomach of the rat. This result is similar to that obtained with the aspirin solution in this study. However, Alphin and Droppleman (5) reported that phenylbutazone produced less ulceration and bleeding in the cat than were produced by aspirin. Phenylbutazone is known as a possible ulcerogenic drug, and its ulcerogenic effect was suggested to be due to reduced mucosal resistance to the erosive action of acid and pepsin.

When phenylbutazone (25 mg) was administered in the powder form, no gastric bleeding and lesions were found in the rats. This was due to poor dissolution of the drug in the stomach; phenylbutazone powder was found in the stomach of the rat after 1 hr.

After the administration of a caffeine solution, there was no evidence of bleeding or the presence of lesions. Little or no irritation was produced by the caffeine on the stomach mucosa of the rat.

None of the rats given triamcinolone powder (20 mg) showed any evidence of bleeding or ulceration of the stomach. Triamcinolone is also known to be ulcerogenic in susceptible humans.

In the final group of rats, food was allowed at least 1 hr before the administration of aspirin solution or aspirin powder. No bleeding or ulceration was seen in any of these rats.

This study indicates that common drugs can cause the production of lesions in the stomach of the rat. One of the most widely used compounds by humans, aspirin, produced irritation, bleeding, and lesion formation upon administration of aspirin powder or solution by mouth in the dose studied. Since aspirin is freely soluble in polyethylene glycol base, this observation suggests that aspirin, when administered in a solution, can cause as much gastric bleeding and ulceration as the administration of a solid form of aspirin. Polyethylene glycol base did not seem to prevent gastric lesions produced by aspirin.

Little or no bleeding or lesion production was seen in the rats that received the aspirin solution rectally. The presence of food in the stomach appears to reduce bleeding and ulcer production usually caused by aspirin.

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