Tablet Absorption in the Rat

Keyphrases ☐ Pharmacokinetics, bioavailability—4-(3′-pyridyl)-bicyclo[2.2.2]octane-1-amine maleate tablets, rats ☐ Tablet absorption—rats ☐ 4-(3′-Pyridyl)bicyclo[2.2.2]octane-1-amine maleate—tablet absorption, rats

Sir:

The current interest in bioavailability data and their requirement by the FDA have necessitated increased effort in the development of biopharmaceutical programs by the pharmaceutical industry. The absorption of a drug from a given dosage form is one important criterion that must be studied early in the development process. Since many products are marketed in tablet form, this dosage form should be compared to parenteral and oral solution administrations. Usually, the dog is the animal of choice for tablet studies because of convenience in dosing with tablets. However, the dog may sometimes be a poor model for preliminary absorption studies because of low excretion of unchanged drug or metabolic differences which do not permit a readily monitored system.

In the present study, the drug under investigation, 4-(3′-pyridyl)bicyclo[2.2.2]octane-1-amine maleate, was not sufficiently recovered from the urine of the dog to permit tablet absorption studies. Since the rat differed from the dog in excreting a significant amount of unchanged drug in the urine, it was used in such a study.

Standard tableting equipment was used to prepare 21-mg., 0.32-cm. (0.125-in.) diameter tablets. The tablets were administered to untrained rats by a relatively simple technique which required two technicians. The equipment required was minimal and readily available.

The special tablets for this rat study were prepared from tablets produced for human clinical use. The tablets for clinical use contained 50 mg. of active ingredient in a tablet of 175-mg. total weight, prepared by a wet granulation process. The special tablets were prepared by comminuting the original tablets in a mortar and then recompressing tablets on a Stokes A-3 single-punch tablet press equipped with a standard concave, 0.32-cm. (0.125-in.) punch and die set. The newly produced tablets contained 6.7 mg. (range 6.4–6.9 mg.) of active ingredient (as assayed by GLC) in a tablet of 21-mg. total weight.

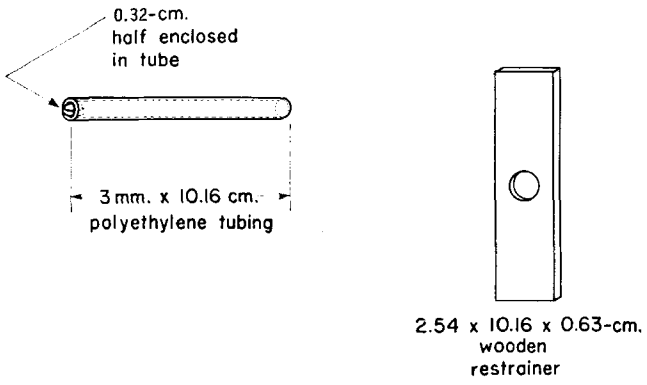

Figure 1—*Rat tablet-dosing apparatus.*

Table I—Relative Absorption Data

Hours Posttreatment	Percent Dose Excreted in Urine as Unchanged Drug		
	Intravenous	Oral Solution	Tablet
0–5	15.6	14.7	9.1
5–12	0.4	1.4	7.8
12–24	0.5	0.4	1.1
24–29	0.1	0.3	0.1
29–48	0.0	0.0	0.1
Total	16.6	16.8	18.2

n = 24 rats/dosage form

It was found that 200-g. rats were the minimum size necessary for dosing with the 0.32-cm. (0.125-in.) tablet. The tablet was partially secured inside a 3-mm. i.d. × 10.16-cm. (4-in.) section of polyethylene tubing (Fig. 1) by pressing the tubing down over about one-half of the tablet. The rat was held in the technician's left hand, and the mouth of the rat was held open by use of a 2.54 × 10.16 × 0.63-cm. (1 × 4 × 0.25-in.) section of wood with a 1.27-cm. (0.5-in.) hole drilled in the center. The hole was centered in the rat's mouth. The second technician slid the polyethylene tubing containing the tablet through the hole in the wooden guide and into the esophagus (similar to using an intubation cannula). A silver cannula was inserted into the tubing to push the tablet away and down the esophagus of the rat. The rat showed no sign of discomfort during the treatment. No sign of rupture or internal bleeding was seen. Necropsy of the rat immediately after dosing showed that the tablet reached the stomach intact.

Table I lists relative absorption data for three different dosage forms of the compound. The data show that the tablet was well absorbed in the rat. Despite the relatively low excretion of unchanged drug in the urine, the data demonstrate that the tablet dosage form can be successfully used in the rat.

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