Duodenal Fistula Dog as Test Animal for Acid-Stable or -Labile Compounds.* (23008)

CHENG-CHUN LEE. (Introduced by K. K. Chen)
The Lilly Research Laboratories, Eli Lilly and Co., Indianapolis, Ind.

The pharmacologic assay of certain orally administered drugs is handicapped by the fact that the drugs are partially or completely destroyed by the gastric acids. In order to overcome this difficulty, duodenal fistula dogs have been prepared for the testing of such compounds. The procedure is described in this communication.

Material and methods. Duodenal fistula dog. Healthy female mongrel dogs were anesthetized with an intravenous dose of 30 mg of sodium pentobarbital per kg body weight. The inner part of a Lucite Thomas intestinal fistula(1) was placed into the duodenum about 2 inches from the pyloric opening; the outer part was inserted in a lateral abdominal incision about one inch to the right of the mid-line and one inch from the last rib. Five fistula dogs† weighing between 10.2 and 16.5 kg, were used in these studies. They were operated on 44, 40, 7, 4 and 2.5 months prior to these experiments. *Testing material.* The antibiotic erythromycin‡ was chosen because it possesses properties that make it especially suitable for the tests: First, erythromycin is absorbed through the gastrointestinal tract (2). Second, erythromycin B is more acid-resistant than erythromycin A(3); both were used in these studies for comparison. Third, the serum and urine concentration of erythromycin can be readily assayed by a cup plate method(4). The erythromycin A used in these studies assayed 956 μg/mg, and the erythromycin B assayed 637 μg/mg. They were given in capsules on weight basis. All dogs were starved overnight and single doses of erythromycin administered either by mouth or through the fistula. Each animal received water by stomach tube, 25 ml/kg at the beginning of the experiment and 10 ml/kg 2 hours later. This arbitrary procedure was to insure sufficient output of urine. At intervals, blood was drawn from the jugular vein and urine was collected in graduated cylinders at the end of the second and the sixth hour. Erythromycin was assayed on the serum and on the urine appropriately diluted with physiological saline, against standard curves based upon horse serum and physiological saline, respectively. The dogs were allowed to rest for one week before the experiments were repeated.

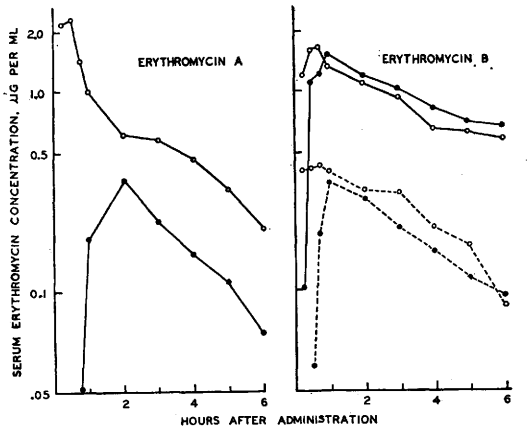

FIG. 1. Serum erythromycin levels following oral (dots) and intraduodenal (open circles) administration. Solid lines, 20 mg/kg; interrupted lines 5 mg/kg.

Results. The average erythromycin serum levels of 5 duodenal fistula dogs are shown in Fig. 1. After intraduodenal administration of 20 mg/kg of erythromycin A, the serum level reached a peak within 30 minutes. It dropped rapidly during the first hour and declined rather slowly thereafter. After the same oral dose, on the other hand, the serum level was much lower, indicating considerable destruction of erythromycin A in the stomach. In this case, the peak of the serum level was not reached until about 2 hours after admin-

* The author wants to thank R. O. Froman for his technical assistance; D. W. Ziegler and Stanis Stroy for penicillin assays.

† The cystic duct of these dogs was tied off with braided silk during operation for the purpose of hepatic bile collection in other studies.

‡ The trademark of Eli Lilly and Co. for the antibiotic erythromycin is 'Ilotycin'.

TABLE I. Urinary Recoveries of Erythromycin 6 Hours after Administration.

Erythromycin	Dose, mg/kg	% of dose* Oral	% of dose* Intraduodenal
A	20	2.4 ± .9	7.6 ± 1.3
B	20	15.9 ± 2.0	9.8 ± 1.6
B	5	9.5 ± 1.0	12.6 ± 2.2

* Avg and stand. error.

istration and the serum concentration at the end of 6 hours was only one-fourth of that obtained after intraduodenal administration.

When erythromycin B was given to these 5 duodenal fistula dogs, the serum concentrations reached about the same peak after oral and after intraduodenal administration. After oral administration of 20 mg/kg, the maximal serum concentration was obtained at one hour, whereas the peak was reached about 15 minutes earlier when the drug was administered into the duodenum. In both cases, the serum erythromycin concentration declined slowly thereafter. Oral and intraduodenal administrations of 5 mg/kg of erythromycin B resulted in identical serum concentration curves. This clearly demonstrates that erythromycin B is acid-resistant.

The urinary recoveries of erythromycin A and B are summarized in Table I. An average of 2.4 ± 0.9% of erythromycin A was recovered 6 hours after oral administration and an average of 7.6 ± 1.3%, after intraduodenal administration. Much larger recoveries were obtained with erythromycin B, 9.5 to 15.9% of the dose when given orally and 9.8 to 12.6% when administered to the duodenum. This again shows that the gastric acids have no apparent effect on the absorption of erythromycin B given orally.

Discussion. The use of duodenal fistula dogs as test animals for acid-stable or -labile compounds has many advantages and is practical. First, an unanesthetized animal is used. Second, a compound can be given to the same dog orally or intraduodenally. Third, the fistula dogs can be used again and again. Fourth, by administration to the duodenum through the fistula, it can readily be determined whether a compound is absorbed through the intestinal tract at all. Fifth, the effectiveness of a special coating agent for acid-labile compounds can be checked. Sixth, the usefulness of various buffer agents added to acid-labile compounds can be tested.

Summary. The usefulness of duodenal fistula dogs as test animals for acid-stable or -labile compounds is demonstrated and the practical application is discussed.

1. Thomas, J. E., PROC. SOC. EXP. BIOL. AND MED., 1941, v46, 260.

2. Lee, Cheng-Chun, Anderson, R. C., and Chen, K. K., *Antibiotic and Chemotherapy,* 1954, v4, 926.

3. Pettinga, C. W., Stark, W. M., and Van Abeele, F. R., *J. Am. Chem. Soc.,* 1954, v75, 569.

4. Kirshbaum, A., Bowman, F. W., Wintermere, D. M., and Friedman, E. R., *Antibiotic and Chemotherapy,* 1953, v3, 537.

Received January 18, 1957. P.S.E.B.M., 1957, v94.