Nasal Absorption of Propranolol in Rats

Keyphrases □ Propranolol—nasal absorption, rats, compared to oral and intravenous dosage forms, bioavailability □ β-Adrenergic blocking agents—propranolol, nasal absorption, compared to oral and intravenous dosage forms, rats, bioavailability □ Dosage forms, nasal—propranolol, absorption, compared to oral and intravenous dosage forms, rats, bioavailability

To the Editor:

Propranolol, the adrenergic β-receptor blocking drug, is widely used for hypertension management and angina pectoris treatment. The drug, however, is inefficiently and variably absorbed from oral dosage forms. A study in humans showed that the oral administration of propranolol results in considerable variation in plasma drug levels. Peak plasma levels in five subjects given 80-mg oral doses varied by sevenfold, while 10-mg iv doses in the same subjects varied by only twofold (1). Furthermore, drug bioavailability of an 80-mg oral dose in some subjects, as calculated from the ratio of the area under the curve, was as low as 16% of the bioavailability of a 10-mg iv dose. The variations in the blood levels as well as the low bioavailability for oral doses have been attributed to the extensive drug metabolism in the GI tract during absorption and/or to the first-pass effect (2, 3).

To enhance drug bioavailability and to minimize blood level variations from the nonparenteral route, drug availability from a nasal solution was investigated. Previous studies in rats, dogs, and humans showed that insulin is efficiently absorbed from the nasal mucosa (4–6).

Sprague–Dawley male rats, ~270 g, were used. For nasal administration, the rats were anesthetized with pentobarbital sodium (50 mg/kg). Drug administration to the nasal cavity with a micropipet, using two doses of 1 and 2 mg/rat in 0.1 ml of pH 7.2 isotonic buffer, was carried out according to the procedure described by Hirai *et al* (4). For intravenous administration, the rats were anesthetized and 1-mg doses of the drug in 0.2 ml of pH 7.2 isotonic buffer were injected through the femoral vein. After the intravenous and nasal administrations, blood was sampled from the femoral aorta periodically.

For oral administration, the rats were not anesthetized and 1-mg doses in 1 ml of pH 7.2 isotonic buffer were administered by a stomach tube. After oral administration, blood was sampled from the tail vein periodically. The blood drug levels were determined spectrophotofluorometrically by a minor modification of the method of Suzuki *et al.* (3).

Figure 1 shows the mean blood propranolol levels for the three administration routes. The blood drug levels after intravenous and nasal administrations of 1-mg doses were identical, whereas the oral administration resulted in considerably lower blood levels. The oral bioavailability calculated from the ratio of the area under the curve, (oral/intravenous) × 100 and (oral/nasal) × 100, within 4 hr was ~15%.

Furthermore, the area under the blood drug level curve was directly proportional to the dose administered nasally (Fig. 1). The results also indicate that propranolol is rapidly absorbed from the nasal mucosa. The peak plasma level was attained within 5 min of nose drop instillation.

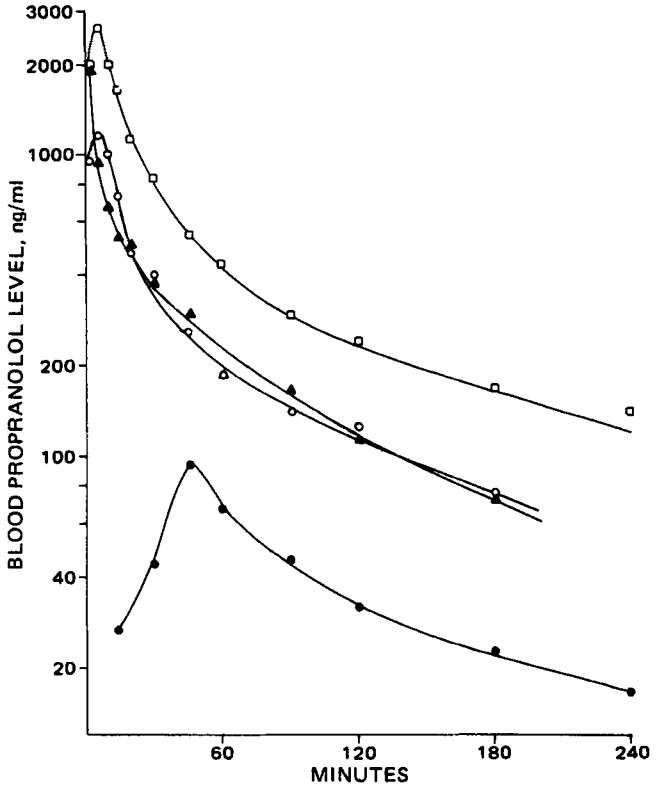

Figure 1—*Time course of the average blood propranolol levels in three rats after nasal administration of 1 mg/rat (○), intravenous administration of 1 mg/rat (▲), oral administration of 1 mg/rat (●), and nasal administration of 2 mg/rat (□).*

The nasal route for propranolol administration appears to be superior to the oral route and as effective as the intravenous route. A study is underway to examine propranolol bioavailability from nasal solutions in dogs.

(1) D. G. Shand, E. M. Nuckolls, and J. A. Oates, *Clin. Pharmacol. Ther.*, **11**, 112 (1970).

(2) C. T. Dollery and D. S. Davies, *Ann. N.Y. Acad. Sci.*, **179**, 109 (1971).

(3) T. Suzuki, Y. Saitoh, S. Isozaki, and R. Ishida, *Chem. Pharm. Bull.*, **20**, 2731 (1972).

(4) S. Hirai, T. Yashiki, and T. Matsuzawa, presented at the 98th Annual Meeting of the Pharmaceutical Society of Japan, Okayama, Japan, Apr. 1978.

(5) S. Hirai, T. Ikenaga, and T. Matsuzawa, *Diabetes*, **27**, 296 (1978).

(6) T. Yokosuka, Y. Omori, Y. Hirata, and S. Hirai, *J. Jpn. Diabetic Soc.*, **20**, 146 (1977).

Anwar A. Hussain ˣ
Shinichiro Hirai
Rima Bawarshi
College of Pharmacy
University of Kentucky
Lexington, KY 40506

Received March 16, 1979.
Accepted for publication June 1, 1979.

0022-3549/79/0900-1196$01.00/0