l-Bunolol and Propranolol: Oral and Intravenous β-Adrenoceptor Blocking Activity in Rats Compared to Dogs and Humans

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Abstract □ To determine the pharmacological significance of reported differences between species in *l*-bunolol metabolism, oral and intravenous β-adrenoceptor blocking activity against an isoproterenol-induced tachycardia was compared in dogs, rats, and humans. Propranolol was similarly studied in rats and dogs. Species differences in intravenous potency were minimal for both compounds in contrast to oral dose studies. Oral to intravenous ratios of doses causing a comparable degree of β-adrenoceptor blockade after *l*-bunolol were: rat, 212; dog, 4; and human, 5. For propranolol, the oral to intravenous dose ratios were 210 and 32 for the rat and dog, respectively. These pharmacological findings show major differences in the rat compared to dogs and humans and may be explained in part by differences in the urinary excretion patterns of *l*-bunolol in the various species.

Keyphrases □ *l*-Bunolol—β-adrenoceptor blocking activity compared in dogs, rats, and humans, oral and intravenous dosage □ Propranolol—β-adrenoceptor blocking activity compared in dogs and rats, oral and intravenous dosage □ β-Adrenoceptor blocking activity—*l*-bunolol and propranolol compared in dogs, rats, and humans, oral and intravenous dosage □ Antiadrenergic agents—*l*-bunolol, β-adrenoceptor blocking activity compared in dogs, rats, and humans, oral and intravenous dosage

l-Bunolol is a potent β-adrenoceptor antagonist undergoing extensive clinical investigation for treatment of hypertension, angina, and arrhythmia. There are major differences in the urinary excretion patterns of *l*- (and *dl*-) bunolol and its metabolites after oral dosing in the rat (1, 2), dog (1, 3), and human (1, 4, 5). The presence of recognized active metabolites in rat urine is substantially reduced as compared to the dog and human. These observations suggest that the rat, because of its unique metabolism, may be more resistant to the β-adrenoceptor blocking activity of orally administered *l*-bunolol than are the other two species. Therefore, the β-adrenoceptor blocking dose of *l*-bunolol after intravenous and oral administrations to the rat was determined, and the data were compared to those previously reported for the dog (6) and human[1]. Similar comparisons were also made with propranolol[2].

EXPERIMENTAL

Oral Dose Studies—Two hours prior to the induction of pentobarbital (58 mg/kg ip) anesthesia, separate groups of 24-hr fasted, male Sprague–Dawley rats[3], 260–388 g, were dosed by gavage with aqueous solutions of *l*-bunolol (0.1, 0.3, 1, and 3 mg of base/kg), propranolol (1, 3, 10, and 30 mg of base/kg), or lactose (0.1 mg/kg) (control). Drugs and lactose were dissolved in distilled water, and the volume of administration was 0.1 ml/100 g of body weight. After anesthesia, heart rate was recorded[4] from a cardiotachometer, which was triggered by the R wave of the lead II electrocardiograph.

Isoproterenol (0.025 μg total dose) was injected *via* a catheterized tail vein 2.5, 3, and 3.5 hr after oral drug or lactose administration. The isoproterenol dose selected caused reproducible, submaximal tachycardic responses of 87 ± 12 (*SEM*) beats/min in the control group of animals. Potency values were calculated at 3 hr after drug administration since maximal inhibition of isoproterenol usually occurred at this time.

Intravenous Dose Studies—Inhibition of isoproterenol-induced tachycardia also was determined after single intravenous doses of *l*-bunolol (3, 10, and 30 μg/kg) and propranolol (10, 30, and 100 μg/kg) to separate groups of anesthetized rats. The standard intravenous isoproterenol challenge was given before and 10 min after drug administration.

Potency values in the oral dose study were based on the average heart rate response to isoproterenol produced in the control (lactose) group of animals; in the intravenous dose study, each animal served as its own control. Data were analyzed using a weighted linear regression format and the Student *t* test (7). A *p* value of <0.05 was regarded as significant.

Table I—*l*-Bunolol and Propranolol: Intravenous and Oral β-Adrenoceptor Blocking Doses in Rats

Route	*l*-Bunolol, μg/kg		Propranolol, μg/kg	
	ID_{50}[a]	Relative Activity[b]	ID_{50}	Relative Activity
Intravenous	11 (8–17)		41 (32–55)	
		212[c] (134–338)		210[c] (146–297)
Oral	2390 (1749–4590)		8688 (6720–11,083)	

[a] Dose (micrograms per kilogram) required to cause a 50% inhibition of the tachycardic response to 0.025 μg of isoproterenol (95% confidence limits). Each value represents results from at least four animals. [b] Oral to intravenous dose ratio (95% confidence limits). [c] $p < 0.05$.

RESULTS AND DISCUSSION

The intravenous and oral doses of *l*-bunolol and propranolol in rats required to inhibit an isoproterenol-induced tachycardia by 50% are presented in Table I. Large multiples (>200) of the intravenous ID_{50} dose of *l*-bunolol and propranolol were required orally to cause comparable pharmacological effects in rats. For comparison, oral to intravenous dose ratios also were computed for the dog and human (Table II). Clinical data for propranolol were derived from the literature (8–11). Factors other than absorption apparently are involved, since both *l*-bunolol (1–5, 12) and propranolol (10, 13, 14) are virtually completely absorbed after oral administration in each species.

The rat, unlike the dog or human, was highly resistant to β-adrenergic receptor blockade by oral treatment with *l*-bunolol. One explanation could be a rapid and extensive biotransformation of *l*-bunolol (and other β-adrenergic blockers) to inactive or conjugated polar metabolites. The large separation in oral to intravenous milligram potency is not unique to *l*-bunolol but was also observed for propranolol (this study, 15), me-

[1] Unpublished observations by Dr. John W. Wallace (Cardiology Division, Department of Internal Medicine, University of Texas Medical Branch at Galveston, Galveston, TX 77550) on file at Warner-Lambert Research Institute, Morris Plains, NJ 07950.

[2] All references to propranolol used throughout the text refer to the *dl* or racemic form of the compound.

[3] Charles River.

[4] Beckman type R dynograph.

Table II—*l*-Bunolol and Propranolol: Comparative Oral to Intravenous Dose Ratios in Rats, Dogs, and Humans

Species	*l*-Bunolol	Propranolol
Rat	212 (Table I)[a]	210 (Table I)
Dog	4 (6)	32 (6)
Human	5[b]	8–20 (8–11)

[a] Appropriate reference citations are in parentheses. [b] Unpublished observations.

toprolol (16), labetalol (17), and other β-blockers (18) and has been ascribed in part to unique metabolism in the rat.

Other factors such as presystemic (first-pass) elimination (*e.g.*, hepatic extraction) warrant consideration. Previous studies in the dog (19) showed that *l*-bunolol underwent relatively little presystemic inactivation compared to propranolol. These results are consistent with the large differences in oral to intravenous dose ratios reported in the dog and human for propranolol compared to *l*-bunolol (Table II). In the rat, the oral to intravenous dose ratios for *l*-bunolol and propranolol were virtually identical, 212 and 210, respectively. Therefore, some presystemic or extrahepatic mechanism may be operative for *l*-bunolol in the rat (unlike the dog), as was reported for propranolol in this species (20, 21).

Based on the urinary excretion patterns of *l*-bunolol and its active metabolite dihydrobunolol in the rat and dog (22) (Table III), the observed oral to intravenous potency differences between the two species were greater than expected. Therefore, other undefined differences must account for the low oral potency of *l*-bunolol in the rat. Comparative pharmacological studies on hydroxydihydrobunolol (Table III) (2, 3), which is expected to be an active metabolite, have not been performed. Such a study would be of interest; however, the compound is presently unavailable in adequate quantities.

These studies indicate that large oral doses of *l*-bunolol, propranolol, and, presumably, most other β-blockers are required to achieve β-adrenoceptor blockade in the rat. Failure to recognize this species difference could result in the misinterpretation of experimental data when oral doses of β-blockers are used in the rat.

Table III—Identified Active Compounds of Oral Bunolol in Pooled Urine[a] (0–24-hr Collection)

Species	Oral Dose, mg/kg	Percent of Dose Excreted		
		Bunolol	Dihydrobunolol	Hydroxydihydrobunolol[b]
Rat	10	0.09	0.02	0.15
Dog	10	0.4	0.3	6.0
Human	~0.04[c]	12.9	23.7	1.8

[a] Values were obtained from Di Carlo *et al.* (1). [b] Hydroxydihydrobunolol has not been evaluated pharmacologically; whether or not pharmacological data on this urinary metabolite will account for the low oral potency in the rat remains to be established. [c] A 3-mg total dose. The mean body weight of subjects was 74.1 ± 6.6 kg.

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