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Comparative Cardiovascular Effects of Propranolol and Practolol in Puppies[1] (39208)

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(Introduced by J. S. C. Wang)

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The cardiovascular effects of the beta blocking agents propranolol and practolol have been studied in adult patients at cardiac catheterization (1, 5, 13, 19) as well as in adult animals (8, 10, 20) in the experimental laboratory. It has been shown that propranolol produces direct, progressive myocardial depression as beta-blocking doses ae exceeded (1, 4, 6, 9). Propranolol has also been demonstrated to increase peripheral vascular resistance (2) and to prolong atrioventricular conduction (6, 17, 18). Practolol has similar beta-blocking effects at one-third to one-quarter of the potency of propranolol (4, 10). However, practolol does not produce myocardial depression in large doses (6, 9), is not associated with increases in peripheral resistance (4), and does not alter atrioventricular conduction when administered beyond beta-blocking dosage (6, 17, 18).

The effect of propranolol on mature and immature cardiac muscle has been studied in isolated preparations of fetal and adult myocardium in lambs (7) as well as in intact puppies and adult dogs (21). These investigations have indicated that propranolol is a more potent depressant of the immature circulation than of the adult cardiovascular system. The cardiocirculatory effects of practolol in very young animals have not been described.

It is the purpose of the present investigation to study sympathetic beta blockade in puppies utilizing propranolol and practolol, and to delineate the effect of large doses of these agents on cardiovascular function.

Methods. Twenty-one mongrel puppies (3 to 4 weeks old) weighing 1.4 to 1.9 kg were anesthetized with choralose (50 mg/kg) and morphine (1 mg/kg). The animals were ventilated with room air at a tidal volume of 12–20 ml by means of a mechanical respirator (Harvard Apparatus Co., Millis, Massachusetts). A polyethylene catheter was inserted into the external jugular vein, advanced to the right ventricle, and connected to a Medtronic stimulator. A No. 5 catheter tip micromanometer (Millar Instrument Co., Dallas, Texas) was inserted into a carotid artery and advanced under fluoroscopic visualization to the left ventricle. A No. 5 Lehman catheter on a Statham P-23 db strain gauge was inserted into the other carotid artery and advanced initially to the left ventricle to calibrate the catheter tip manometer. It was then withdrawn to record pressures in the ascending aorta. Cardiac output was measured by the indicator dilution technique (Fig. 1). Indocyanine green dye was injected into the right atrial catheter and arterial blood was withdrawn from the aortic catheter through a cuvette densitometer (Model XP 302, Waters Co., Rochester, Minnesota), at a rate of 8 ml/min. The blood was returned to the animals through a second venous catheter in the opposite jugular vein by means of a polystaltic pump (Buchler Instrument, Inc., Fort Lee, N.J.), thereby avoiding changes in the circulating blood volume. Heart rate, left ventricular peak systolic pressure, *dp/dt*, left ventricular end-diastolic pressure (LVEDP), and aortic pressure were recorded on an Electronics for Medicine model DR-8 oscillograph as previously described (21). A continuous recording of *dp/dt/P* was obtained electronically by the method of Grossman *et al.* (11). Pressure tracings, LV *dp/dt*, and LV *dp/dt/P* were recorded photographically at a paper speed of 100 mm/sec.

Dose response curves. Propranolol was administered in doses of 0.1, 0.2, 0.3, 0.6, 1.2, and 2.4 mg/kg at intervals of 10 to 15

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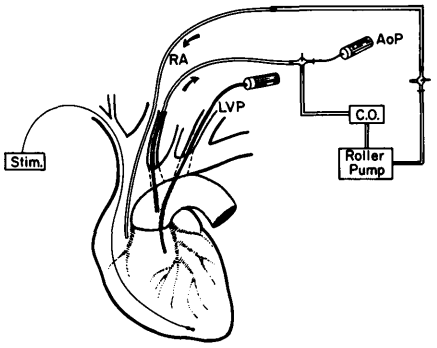

FIG. 1 Diagrammatic representation of the experimental preparation: A catheter tip manometer (thick, dark line) is positioned in the left ventricle. A No. 5 Lehman catheter is located in the aortic root. A pacing catheter is shown in the right ventricle attached to a stimulator (stim). AoP, transducer for measurement of aortic pressure; CO, cuvette densitometer for cardiac output determination; RA, catheter in right atrium; LVP, catheter tip manometer for measurement of left ventricular pressure.

min in nine puppies. Measurements were obtained in the control state and 7 min after each dose of propranolol in order to allow maximum hemodynamic effect. During the dose response curves, a total of 9–10 ml of saline was administered in order to maintain catheter patency, and 2 to 4 mEq/kg of sodium bicarbonate was given, when required to maintain normal acid-base status. No other drugs or fluids were utilized.

In four of the animals, beta blockade was tested at each point on the dose response curve by administration of 0.12 μg/kg/min of isoproterenol for 5 min. Hemodynamic measurements were obtained prior to and after the isoproterenol infusion. When the adrenergic effects of isoproterenol were completely blocked by a dose of propranolol, isoproterenol was no longer administered.

Similar experiments were carried out in 12 puppies utilizing practolol in doses of 0.1, 0.3, 0.6, 1.2, 2.4, and 8.4 mg/Kg. Isoproterenol studies were done in four animals.

Results. Dose response curves. Representative examples of dose response curves with isoproterenol infusion in puppies treated with propranolol and practolol are illustrated in Figs. 2 and 3. Propranolol abolished the beta stimulatory effects of isoproterenol on cardiac index, heart rate, *dp/dt/P*, and LVEDP at dosages of 0.3 to 0.6 mg/kg. Beta-blocking effects for practolol were observed when the dosage reached 0.9 to 2.1 mg/kg. The circulatory effects of propranolol in 9 puppies and of practolol in 12, at beta-blocking doses and seven times blocking dosage, are summarized in Table I and Fig. 4.

Propranolol. Beta blockade with propranolol was associated with statistically significant ($P < 0.05$) decreases in heart rate, cardiac index, *dp/dt*, and *dp/dt/P* when compared with controls by paired Student's *t* test. Peak left ventricular pressure, LVEDP,

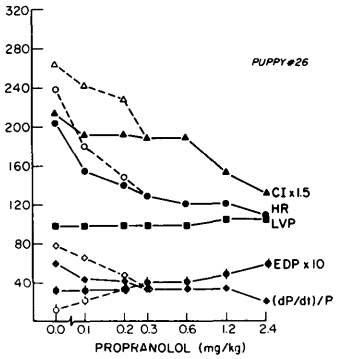

FIG. 2. Representative example of a propranolol dose reponse curve, with isoproterenol (isuprel) infusion. The dashed portion of the curve shows the circulatory effects of 0.12 μ/kg/min of isoproterenol. The blocking level of propranolol is indicated by disappearance of the isoproterenol induced stimulation. CI, cardiac index (ml/kg/min); H.R., heart rate; LVP, left ventricular systolic pressure; EDP, left ventricular end-diastolic pressure; *dp/dp/P*, peak value of ratio of first derivative of LVP to instantaneous LVP. Doses of propranolol in milligrams per kilogram are indicated in the abscissa. A universal scale is shown on the ordinate.

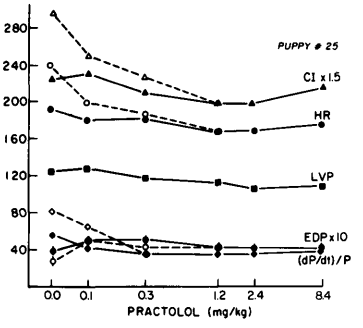

FIG. 3. Representative example of a practolol dose response curve with isoproterenol infusion. Labels as in Fig. 2.

mean aortic pressure, and systemic resistance did not change significantly.

Propranolol (2.1 mg/kg), approximately seven times the blocking dose, produced a significant decrease in heart rate, cardiac index, *dp/dt,* and *dp/dt/P,* compared to 0.3 mg/kg. Systemic resistance index and LVEDP increased significantly. The mean aortic pressure and peak left ventricular pressure were unchanged.

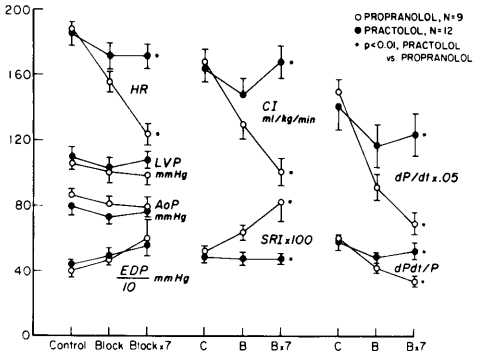

FIG. 4. Cardiovascular effects of practolol (12 puppies) and propranolol (9 puppies) as determined by dose response curves. The dose levels are shown on the abscissa for each parameter: control, blocking level, and maximum (seven times blocking dose). A universal scale is presented on the ordinate. Standard errors are shown in brackets. Statistically significant difference between practolol and propranolol groups are indicated by asterisks for $P < 0.01$. SRI, systemic resistance index.

Practolol. Similar to propranolol, practolol at beta-blocking dosage produced significant decreases in heart rate, cardiac index, and *dp/dt/P,* as compared to control animals, while the other parameters did not change significantly. Administration of 8.4 mg/kg of practolol (7 × beta-blocking dose) produced no further significant hemodynamic changes except for an increase in *dp/dt/P* from 49 + 3 to 53 + 5 sec^{-1}.

Comparison of propranolol and practolol. Hemodynamic data obtained prior to administration of drugs showed no significant differences between the propranolol and practolol groups. Similarly, no statistically significant hemodynamic differences could be demonstrated between the two groups after beta blockade was induced by propranolol or practolol (Table I). However, maximal doses of propranolol (2.1 mg/kg, 7 × blocking dose) produced significant decreases in heart rate, cardiac index, *dp/dt,* and *dp/dt/P* when tested against comparable doses of practolol (8.4 mg/kg, 7 × blocking dose) by Student's *t* test.

Discussion. Previous investigators have emphasized the difficulty in determining the onset of beta blockade in any given animal because of immeasurable variations in basal sympathetic activity. Accordingly, in this study, a known amount of isoproterenol was administered to induce comparable levels of

TABLE I. HEMODYNAMIC EFFECTS OF PROPRANOLOL AND PRACTOLOL IN PUPPIES.[a]

	Practolol (12 animals)			Propranolol (9 animals)		
	Control	Block	Block × 7	Control	Block	Block × 7
Heart rate (beats/min)	192 ± 8 (SE)***	172 ± 8*	171 ± 8(x)	185 ± 5***	155 ± 6*	138 ± 6**(x)
Cardiac Index (ml/min/kg)	165 ± 8	148 ± 10*	168 ± 10(x)	169 ± 8***	130 ± 9*	101 ± 8**(x)
dp/dt (mm Hg/sec)	2817 ± 282	2349 ± 259	2480 ± 270(x)	2998 ± 173***	1825 ± 161*	1395 ± 136**(x)
(dp/dt)/P sec-1	58 ± 5	49 ± 3*	53 ± 5**(x)	60 ± 2***	43 ± 3*	34 ± 3**(x)
LVP (mm Hg)	109 ± 6	103 ± 6	108 ± 5	106 ± 4	101 ± 6	98 ± 6
LVEDP (mm Hg)	4.4 ± 0.3***	4.9 ± 0.5	5.7 ± 0.6	4.0 ± 0.3***	4.8 ± 0.3	6.0 ± 1.5**
AOP (mm Hg)	80 ± 6	73 ± 5	78 ± 4	87 ± 5	81 ± 5	79 ± 6
SRI	0.49 ± 0.03	0.48 ± 0.04	0.48 ± 0.03	0.53 ± 0.03	0.64 ± 0.5	0.83 ± 12

[a] Abbreviations used in table: SE, standard error or mean; LVP, peak systolic pressure in left ventricle; LVEDP, left ventricular end-diastolic pressure; AOP, mean aortic pressure; SRI, systemic resistance; (*dp/dt*)/*P* = Contractile element velocity, determined as peak value of ratio of first derivative of LVP to instantaneous LVP; Block = 0.3 mg/kg of propranolol and 1.2 mg/kg or practotol; Block × 7 = maximum dose studied, 2.1 mg/kg propranolol and 8.4 mg/kg practolol.

Statistical significance by paired Student's *t*-test: * $P < 0.05$, control vs block, ** $P < 0.05$, block vs block × 7, and *** $P < 0.05$, control vs block × 7. By student's *t*-test for unpaired data: (x) $P < 0.01$ practolol vs propranolol.

sympathetic stimulation prior to the induction of beta blockade by propranolol or practolol. Although this dosage by necessity was developed on an arbitrary basis, it appears that meaningful comparisons between the dose response curves in the two groups of animals were achieved. Our observations are similar to previous reports in adult subjects that a three- to fourfold dose of practolol is required to induce beta blockade, as compared to propranolol (4, 10). Dosage required for beta blockade with both agents appear to be somewhat lower in these puppies than the blocking doses reported for adult dogs by Goldstein and his co-workers (9). The present data are thus consistent with previous observations indicating an increased sensitivity of the immature circulation to propranolol (7, 21).

Analysis of ventricular function data is complex, and a variety of methods have been employed (14). Measurement of contractile element velocity has been central to many current approaches to this issue. In the present investigation, $dp/dt/P$ has been considered to represent contractile element velocity and has been reported as peak value during isovolumic systole in each beat analyzed (14). We have not extrapolated to V_{max} in the present study, nor have we attempted to distinguish total and and developed pressure. Possible preload dependence of these parameters is a controversial issue which remains incompletely resolved (12, 14, 15, 22).

Maximal doses of propranolol produced changes indicative of depression of left ventricular contractility, which were not observed with practolol. Indeed, large doses of practolol appeared to improve ventricular performance as determined by the dose response curves. Similarly, studies in adult animals depleted of catecholamines by reserpine have shown that practolol acts as a beta stimulator. In contrast, propranolol exerts a myocardial depressant effect at large dosages which is apparently unrelated to beta receptor sites (6, 9, 10).

In the evaluation of the effect of propranolol and practolol on myocardial contractility, the influence of changes in vascular resistance must be considered. At large doses, propranolol reduces cardiac output, primarily through its direct depressant effect on the heart. However, propranolol also increases peripheral resistance, apparently by unmasking the constrictor properties of circulating epinephrine (1). This property of the drug also contributes to reduction of cardiac output when large doses of the agent are administered. Increases in systemic vascular resistance were not observed with practolol in either the present or in previous investigations (4).

Summary. The present results indicate that in 3–4-weeks-old puppies propranolol induces a significant depression of cardiovascular function expressed by a decrease in heart rate, myocardial contractility, and cardiac output, and an increase in systemic vascular resistance, in doses beyond beta-blocking levels. In contrast, practolol, in the same dose range, did not induce further cardio-circulatory depression, as shown by levels of heart rate, myocardial contractility, and cardiac output similar to the values obtained with beta-blocking doses of this agent.

The cardio-depressant activity observed in puppies with doses of propranolol beyond blocking levels is thought to be due to direct negative inotropic and chronotropic effects of this agent, not related to influences on beta receptor sites. Such effect not observed with practolol at doses well beyond beta-blocking levels suggests that this drug exerts a more selective influence on cardiac sympathetic beta receptors.

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