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Effects of Practolol, a New Adrenergic Receptor Blocking Agent on Cardiovascular Responses

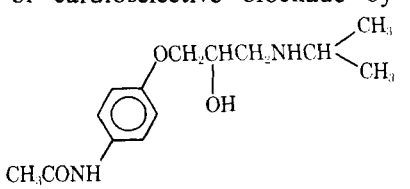
EMMANUEL B. THOMPSON

Abstract □ The claim that practolol, 4-(2-hydroxy-3-isopropylaminopropoxy)acetanilid, is a cardioselective β-adrenergic receptor blocking agent was investigated by testing this compound in cats and in hyperthyroid rabbits for its ability to block certain cardiovascular responses. Doses of 1, 2, 5, and 10 mg./kg. administered intravenously were ineffective in abolishing completely the pressor response to bilateral carotid occlusion. After the administration of either 2, 5, or 10 mg./kg. of this agent, the pressor response due to injected norepinephrine (3 mcg./kg.) was unaffected. However, these doses produced a moderate to marked depression of the increase in chronotropic response caused by the injection of norepinephrine (3 mcg./kg.) and isoproterenol (0.3 mcg./kg.) and the tachycardia attendant with hyperthyroid states. The blockade of the resting tachycardia in hyperthyroid rabbits was significant at all dose levels of practolol ($p \leq 0.01$ or 0.02). Only the 10-mg./kg. dose was found to produce a transient hypotension in cats.

Keyphrases □ Practolol—evaluation as cardioselective β-adrenergic blocking agent □ 4-(2-Hydroxy-3-isopropylaminopropoxy)acetanilid (practolol)—evaluation as cardioselective β-adrenergic blocking agent □ β-Adrenergic blocking agents, cardioselective—practolol evaluation

The introduction into pharmacology of the concept of α- and β-adrenergic receptors by Ahlquist (1) was greatly enhanced by the discovery and continued development of specific antagonists of these receptors. Some of these antagonists, such as dichloroisoproterenol, have been shown to possess an intrinsic β-receptor stimulant action (2–4). Others, such as pronetholol and propranolol, possess, in addition to β-adrenergic receptor blocking action, a cardiac depressant action (5–10). The blocking activity of these compounds is similar qualitatively in that they block all β-adrenergic receptors, but they differ quantitatively.

Recently, a new β-adrenergic receptor blocking agent, 4-(2-hydroxy-3-isopropylaminopropoxy)acetanilid[1] (AY-21,011), (I.C.I. 50,172), or practolol, was shown to possess cardioselective β-blocking activity (11–13). This investigation was undertaken to elucidate further the claim of cardioselective blockade by practolol



practolol

[1] Ayerst Laboratories, New York, N. Y.

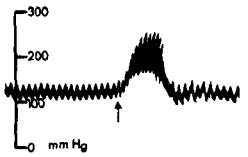


Figure 1—*Bilateral carotid artery occlusion response (30 sec.) in the pentobarbital anesthetized cat. Control conditions prior to any drug administration were: systolic pressure/diastolic pressure = 250/175; corresponding spontaneous heart rate was 170 beats/min.*

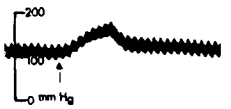


Figure 2—*Bilateral carotid artery occlusion response (30 sec.) 10 min. after intravenous administration of 2 mg./kg. of practolol.*

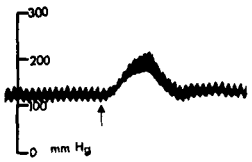


Figure 3—*Bilateral cartoid artery occlusion response (30 sec.) 10 min. after intravenous administration of 5 mg./kg. of practolol.*

through the determination of its effect on some cardiovascular responses involving α- and/or β-receptors. Furthermore, a study was undertaken to determine the effects of practolol on resting tachycardia associated with the hyperthyroid state; since the receptors in the heart are purely β in nature, it is assumed that the adrenergic receptor blocking action of practolol will antagonize this tachycardia.

EXPERIMENTAL

Studies were carried out using rabbits and cats of both sexes, weighing from 3 to 3.5 kg. and 5.0 to 8.0 kg., respectively. In all experiments the animals were anesthetized with sodium pentobarbital[2], 25 mg./kg. A femoral vein and a femoral artery were cannulated for drug administration, and arterial blood pressure was monitored with a pressure transducer[3]. In the cats used, both common carotid arteries were dissected and exposed; the carotid occlusion response was elicited by occluding both common carotid arteries for 30 sec. at an interval of 8 min. The trachea of each rabbit was cannulated, while cuffed endotracheal tubes were used in the cats to facilitate unassisted respiration. The rabbits used in these studies were made hyperthyroid by daily intraperitoneal injections of 100 mg./kg. of *l*-thyroxine for 10–14 days before they were used in the experiments.

The drugs employed in this study included practolol, propranolol, dextropropranolol, isoproterenol hydrochloride[4], and norepinephrine bitartrate[5]. The solutions of drugs were prepared in normal saline for intravenous administration. The doses of drugs mentioned in the text refer to their salts. The measurements were expressed as millimeters of mercury for systolic and diastolic pressures, while the chronotropic responses were in beats per minute. The latter results are the mean ± *SE* for seven hyperthyroid animals.

RESULTS

Effects of Practolol on Response to Bilateral Carotid Artery Occlusion—The effects of 2, 5, and 10 mg./kg. of practolol administered intravenously were determined on the carotid occlusion response in five cats anesthetized with sodium pentobarbital. Both arterial blood pressure and ECG were monitored in each animal. The spontaneous heart rate was obtained directly from the ECG and from a biotachometer[6], triggered by the R-wave of the ECG.

Carotid artery occlusion was instituted for 30 sec., using a serrafine clamp on each carotid artery. Three consecutive occlusions were performed prior to the administration of the initial dose of 2 mg./kg. of practolol. The results obtained from these experiments are given in Table I. Figure 1 shows a typical carotid occlusion response with the corresponding spontaneous heart rate before practolol. In this animal the carotid artery occlusion was 250/175 mm. Hg systolic over diastolic pressure, and the chronotropic response was 170 beats/min. After 2 mg./kg. of practolol, the carotid artery occlusion and spontaneous heart rate were decreased (Fig. 2). The carotid artery occlusion was 175/150 mm. Hg and the heart rate was 150 beats/min. 24 min. after the administration of the blocking drug. These values represent a decrease of 30% of systolic pressure and 14% of diastolic pressure, while the heart rate declined approximately 29%.

Table I—Practolol Effects on Carotid Occlusion Response

Control Response[a]	Dose of Practolol 2 mg./kg.	5 mg./kg.	10 mg./kg.	Experiment Number
123/95	110/80	115/80	152/135	1
180/146	195/150	155/125	200/165	2
250/175	175/150	210/170	220/175	3
180/140	175/135	200/155	200/175	4
162/125	176/145	195/148	195/150	5

[a] Response represents mm. Hg systolic pressure over diastolic pressure.

Figures 3 and 4 show that carotid artery occlusion following 5 and 10 mg./kg. of practolol, respectively, were only slightly affected. The reduction in systolic pressure was only about 12–16%, and there was no change in diastolic response. Although the spontaneous heart rate declined to 100 beats/min. after 5 mg./kg. of practolol, this rate remained constant even with the subsequent increase in dose of the β-blocker. This level of spontaneous heart rate represents a decrease of 60% of the control value.

Effects of Practolol on Responses to Intravenously Administered Isoproterenol—The effect of a dose of 0.3 mcg./kg. of isoproterenol solution administered intravenously was determined on spontaneous heart rate and arterial blood pressure in anesthetized cats. After obtaining three consecutive control responses, the effect of the same dose of isoproterenol was determined in the presence of 1, 2, 5, and 10 mg./kg. of practolol. Isoproterenol was administered 10 min. after the administration of the blocking agent, at two different 10-min. intervals, and in a similar time sequence for each dose of practolol tested.

Practolol in doses of 1, 2, and 5 mg./kg. did not block the hypotensive effect of intravenously administered isoproterenol. However, a dose of 10 mg./kg. of practolol caused transient hypotension due to further enhancement of the blood pressure lowering effects of isoproterenol. The reflex tachycardia usually observed with the hypotensive action of isoproterenol was slightly antagonized by 10 mg./kg., was not affected at all by 5 mg./kg., and was enhanced by 2 mg./kg. of practolol.

Effects of Practolol on Responses to Intravenously Administered Norepinephrine—The changes in chronotropic response and systemic arterial blood pressure to intravenously administered norepinephrine (3 mcg./kg.) was determined in anesthetized cats prior to and after injection of practolol. The procedure used was similar to that described for isoproterenol. All doses of practolol used caused a slight to moderate reduction in chronotropic response but did not effectively lower the pressor response due to norepinephrine injection. In one instance, 10 min. after the administration of 2 mg./kg. of practolol, there was a 37% decrease in chronotropic response following the injection of norepinephrine.

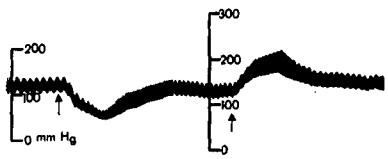


Figure 4—*The hypotensive effect of 10 mg./kg. of intravenously administered practolol and the response to a 30-sec. bilateral carotid artery occlusion 10 min. after the adrenergic receptor blocking agent.*

[2] Nembutal, Abbott Laboratories, Chicago, Ill.
[3] Narco Bio-Systems.
[4] Isoprel hydrochloride, Winthrop Laboratories, New York, N. Y.
[5] Levophed, Winthrop Laboratories, New York, N. Y.
[6] Narco Bio-Systems model BT-1200.

Effects of Practolol on Resting Tachycardia Due to Hyperthyroidism—Rabbits made hyperthyroid by daily intraperitoneal injections of *l*-thyroxine were anesthetized with sodium pentobarbital. Both spontaneous chronotropic response and arterial blood pressure were monitored before and after administration of increasing doses of practolol (1, 2, 5, and 10 mg./kg.) (Figs. 5 and 6). These doses of practolol did significantly ($p \leq 0.01$) reduce the resting tachycardia hyperthyroid state in these animals. The resting tachycardiac rate observed in these animals ranged from 340 to 400 beats/min. In nearly all preparations the initial dose of practolol produced a decreased chronotropic response, usually in the order of 20% of the control. However, subsequent higher doses of practolol failed to decrease further the chronotropic response. The various doses of practolol did not effect any marked reduction in the high systemic arterial blood pressure seen in the hyperthyroid animals (Fig. 7).

Tests of a preliminary nature were conducted with dextropropranolol on the resting tachycardia of hyperthyroid rabbits. It was observed that 5 mg./kg. was lethal and produced a complete heart block; 2 mg./kg. caused an instantaneous hypotension with marked bradycardia and ventricular extrasystoles, which developed into a heart block.

DISCUSSION

The cardioselective action of practolol reported by other investigators (11, 13) was confirmed by the indirect findings of this study. Intravenously administered practolol, in doses of 2, 5, and 10 mg./kg., did not abolish the pressor response to bilateral carotid artery occlusion. However, each dose of the blocking agent caused a slight to moderate suppression of the reflex rise in blood pressure (Figs. 2–4). In a recent study, Abraham *et al.* (14) found that perfusion of small amounts of phentolamine (50–100 ng./kg./min.) intravenously for 1 hr. did not change either the blood pressure or the carotid artery occlusion. However, perfusion of phentolamine through the cerebral ventricles in similar concentrations lowered the blood pressure and depressed the carotid artery occlusion within 20 min. They concluded that the observed effects of phentolamine were central in origin and that the involvement of its peripheral adrenergic receptor blocking action appeared unlikely. Nonetheless, the fact that phentolamine, by its central action, depresses the carotid occlusion response, coupled with its well-known peripheral adrenergic α-receptor blocking property, suggests that the neural pathways involved in the response may have at least one adrenergically mediated synapse. Furthermore, the susceptibility of the response to blockade by phentolamine, and not to propranolol which was also tested, indicated an involvement of α-adrenergic receptors.

If the conclusions of Abraham *et al.* (14) concerning phentolamine are compared with the results reported in the present study with practolol regarding the effect on the carotid artery occlusion, it might be assumed that practolol is devoid of any α-adrenergic blocking action. Moreover, the peripheral β-adrenergic receptor blocking ability of practolol has no involvement on the central mechanism responsible for the pressor response associated with the carotid artery occlusion. Finally, selective reduction in the pressor response to occlusion by propranolol, as reported by Dunlop and Shanks (11), may not be applicable in this respect to practolol, since this effect was not due to a direct blockade of adrenergic β-receptors in the heart but to an indirect one resulting from chronic administration of propranolol. This suggests that practolol may be devoid of any carotid artery occlusion blocking action resulting from direct β-receptor blockade in the heart. The small increase in chronotropic response and the increase in systemic arterial blood pressure following the intravenous administration of 3 mcg./kg. of norepinephrine, coupled with the marked reduction in spontaneous heart rate when 2, 5, and 10 mg./kg. of practolol were given, are consistent with the findings of Adam *et al.* (15), who observed that after practolol (5 mg./kg.), increases in dp/dt and heart rate were either abolished or markedly reduced.

The decline in chronotropic response caused by practolol at the 5-mg./kg. dose level to injected isoproterenol was not very significant. This observation is consistent with that reported by Brick *et al.* (16), who found that in man the increased heart rate produced by intravenous infusion of isoproterenol (3 mcg./min.) for 3 min. was reduced, but the change was not significant. Unlike the present observations and those of Brick *et al.*, Adam *et al.* (15) found that

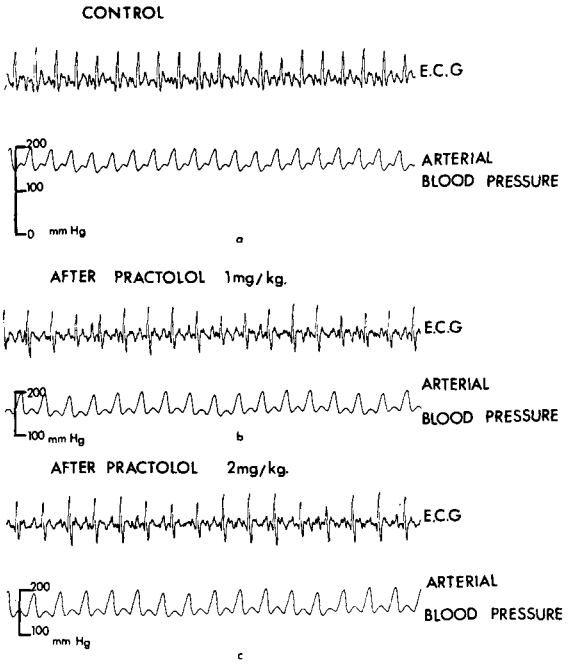


Figure 5—(*a*) *A typical record of rabbit ECG Lead II and arterial blood pressure monitored under control conditions: spontaneous heart rate, 340/min.; systolic pressure, 190 mm. Hg; and diastolic pressure, 145 mm. Hg.* (*b*) *ECG Lead II and arterial blood pressure after 1 mg./kg. of intravenously administered practolol: spontaneous heart rate, 260/min.; systolic pressure, 200 mm. Hg; and diastolic pressure, 150 mm. Hg.* (*c*) *ECG Lead II and arterial blood pressure after 10 min. of an intravenous dose of 2 mg./kg. practolol: spontaneous heart rate, 260/min.; systolic pressure, 200 mm. Hg; and diastolic pressure, 148 mm. Hg.*

practolol (5 mg./kg.) abolished or markedly reduced the tachycardia and the increase in contractility but did not affect the vasodepression caused by isoproterenol. The present studies showed that practolol (10 mg./kg.) markedly reduced the chronotropic response to injected isoproterenol. Further reduction in the vasodepressor action of isoproterenol was also observed with all doses of practolol employed. No explanation can be advanced for the difference in these findings and those of Adam *et al.* for the response to isoproterenol observed at the 5-mg./kg. dose level of practolol. Although different animal species were used in these studies, it is unlikely that species difference was a contributing factor, since cats

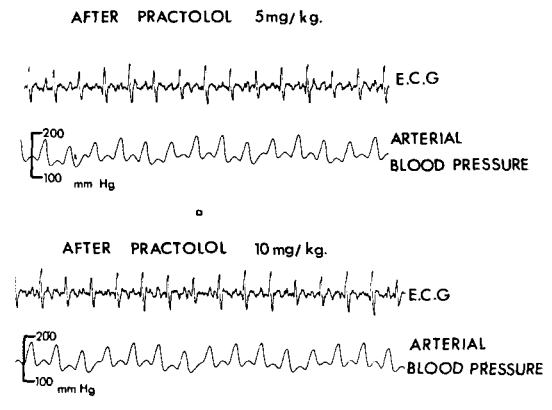


Figure 6—(*a*) *ECG Lead II and arterial blood pressure 10 min. after 5 mg./kg. i.v. of practolol: spontaneous heart rate, 260/min.; systolic pressure, 185 mm. Hg; and diastolic pressure, 130 mm. Hg.* (*b*) *ECG Lead II and arterial blood pressure 10 min. after 10 mg./kg. i.v. of practolol: spontaneous heart rate, 260/min.; systolic pressure, 180 mm. Hg; and diastolic pressure, 130 mm. Hg.*

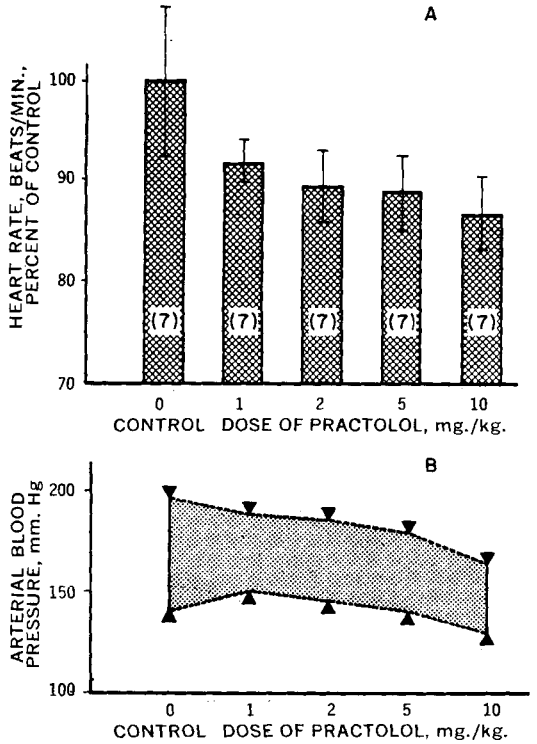


Figure 7—*(A) The effect of four different doses of practolol (1, 2, 5, and 10 mg./kg.) on the spontaneous heart rate in beats/min. resting tachycardia in hyperthyroid rabbits. The number in parenthesis corresponds to the number of animals used in this study. Key: 1 mg./kg., $p < 0.01$; 2 and 5 mg./kg., $p < 0.02$; and 10 mg./kg., $p = 0.01$. (B) The effect of increasing doses of practolol (1, 2, 5, and 10 mg./kg.) on systemic arterial blood pressure in mm. Hg in hyperthyroid rabbits. Key: ▼- - -▼, systolic pressure; and ▲- - - ▲, diastolic pressure. Each point is the average of seven observations.*

and dogs have been known to show a similar depressor response to injected isoproterenol and various types of β-adrenergic receptor blocking drugs.

The tachycardia associated with the experimental hyperthyroid state was used as an index of determining the cardioselective action of practolol in rabbits. This tachycardia was significantly reduced by all doses of practolol tested (Fig. 7A). The attendant hypertension, however, was not markedly reduced by these doses of practolol. Only 10 mg./kg. produced a significant fall in systolic arterial pressure and a moderate fall in diastolic pressure. This latter finding is particularly interesting from the point of view that systolic pressure is usually an index of stroke volume while diastolic pressure reflects total peripheral resistance. The marked effect of practolol (10 mg./kg.) on systolic pressure may be due to its β-adrenergic blocking effect on the receptors of the heart. The lack of a marked effect on diastolic pressure may be due to its inability to alter peripheral resistance. This view is in agreement with that of Ross and Jorgensen (17), who found that practolol, in amounts that blocked the increase in myocardial contractile force due to catecholamines, did not directly affect the coronary vascular β-adrenoceptors which are more resistant to blockade with practolol than are the β-adrenoceptors of the myocardium.

The reduction of tachycardia in the hyperthyroid condition by practolol suggests that: (*a*) an adrenergic component is involved in the mechanism of this tachycardia, (*b*) adrenergic β-receptors, which were probably stimulated by increased levels of catecholamines due to the hyperthyroid state, became much more susceptible to the blocking action of practolol at these doses, and (*c*) because of the cardioselective action of practolol, it might be possible to prevent force and rate changes in the heart without affecting vascular responses to various forms of adrenergic stimulation.

SUMMARY

Practolol (AY-21,011) (I.C.I. 50,172) was studied for its cardioselective blockade of adrenergic receptors in the heart. It has a relatively weak action in blocking the vasodilator effects of catecholamines and the pressor response due to bilateral carotid artery occlusion. Practolol profoundly reduces the tachycardia induced by the intravenous administration of isoproterenol or by experimental hyperthyroidism induced in rabbits.

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