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Beta-Adrenergic Blockade and Antiarrhythmic Activity of (—)- and (+)-Propranolol

by

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Some beta-adrenergic blocking drugs have been shown to reverse clinical as well as experimentally-induced cardiac arrhytmias. However, there appears to be no correlation between antiarrhythmic and beta-blocking activity. The antiarrhythmic effect seems to be accounted for by either local-anesthetic or quinidine-like properties. The clinical use of beta-blocking drugs in cardiac arrhythmias is clearly limited by the overall adrenergic blockade that may lead to cardiac failure. But since beta-blocking and antiarrhythmic activities do not depend on the drug interaction with the same receptor, an effort is being made to find out the moiety responsible for the antiarrhythmic action. Howe and Shanks (7) reported that (+)-propranolol had one sixtieth to one hundredth of the beta-blocking potency of the (—)-propranolol, but the dextro isomer was much more effective in reverting ouabain-induced cardiac arrhythmias of anesthetized cats. However, no difference was found between the local anesthetic potency of both isomers (9). Different results were obtained by other investigators. The antiarrhythmic activity of (+)-propranolol was shown by Parmley and Braunwald (12) to be similar to that of the racemic mixture in ouabain-induced cardiac arrhythmias of rabbits. Barret and Cullum (2) reported that (+)-propranol was as effective as the levo isomer insofar as local anesthetic activity is concerned, but was less potent in reverting the ventricular tachycardia induced by ouabain in anesthetized cats and dogs. Preliminary studies performed in the students laboratory work showed that, in some anesthetized dogs, (+)-propranolol failed to convert ouabain-induced ventricular tachycardia into sinus rhythm. A systematic study, therefore, was undertaken to compare (+)- and (—)-propranolol with regard to their antiarrhythmic and beta adrenergic blocking activity in anesthetized dogs.

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Materials and Methods

Twenty four adult dogs of either sex, weighing from 8 to 15 kg, were anesthetized with intravenous sodium pentobarbital (30 mg/kg). Additional doses were occassionally required to maintain light anesthesia. A femoral artery was exposed and catheterized for blood pressure recordings. Arterial pressure was continuously monitored with a membrane manometer on a Harvard Chart Mover. An indwelling catheter in the cephalic vein was used for drug injections. Needle electrodes were inserted subcutaneously and the electrocardiographic tracings, obtained from either lead II or III, were recorded on thermosensitive paper. The paper speed was maintained at 25 mm/sec.

BETA-RECEPTOR BLOCKADE. Eight dogs were injected with increasing doses of one of the propranolol isomers. Changes in blood pressure and heart rate were evaluated fifteen minutes after each injection. Control dose-response curves for the positive chronotropic and vasoactive effects of isoproterenol were obtained. Following the administration of the propranolol isomer, the dose-response curves were repeated.

OUABAIN-INDUCED ARRHYTHMIAS. Doses of 10 μg/kg of ouabain were injected intravenously at regular intervals of 5 min until ventricular tachycardia was induced. When the arrhythmia persisted for at least 5 min, the propranolol isomer was injected at a rate of 0.4 mg/kg/min, until the sinus rhythm was restored. Whenever the ventricular tachycardia reappeared, the propranolol isomer was again administered until the sinus rhythm was maintained for a minimum of 30 min, or a marked fall in blood pressure was evident.

DRUGS. The following drugs were used: (+)- and (—)-propranolol hydrochloride (ICI-Farma); (±)-isoproterenol hydrochloride (Boehringer Sohn Ingelheim); ouabain (Nativelle); sodium pentobarbital (Abbott).

Results

BETA BLOCKING ACTIVITY. The effects of (+)- and (—)-propranolol on the resting heart rate and PR interval of pentobarbitalized dogs were dose-dependent (fig. 1). (—)-Propranolol was clearly more potent than (+)-propranolol in reducing cardiac frequency; maximum bradycardia was reached at the dose of 2.5 mg/kg of the levo isomer, whereas a plateau could not be attained with a dose of 10 mg/kg of the dextro isomer.

PR interval was significantly increased by the two isomers, and the effect of (—)-propranolol was slightly greater than that of (+)-propranolol; the differences, however, were not statistically significant at any dose level. 3 out of 4 dogs died

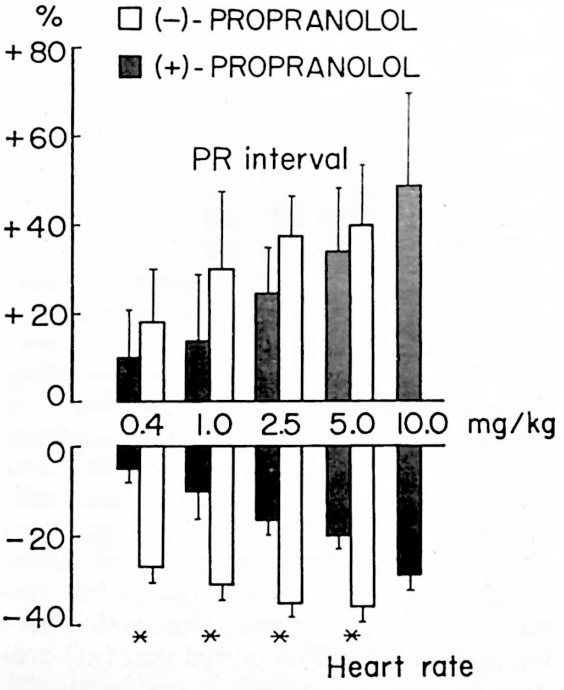

FIG. 1. Effects of cumulative doses of (—)- and (+)-propranolol on the heart rate and PR interval of anesthetized dogs. Each bar represents mean values ± S.D. for four animals. An asterisk indicates a statistical significance ($p < 0.05$) of the difference between the values corresponding to each isomer. For effects of 10 mg/kg, see the text.

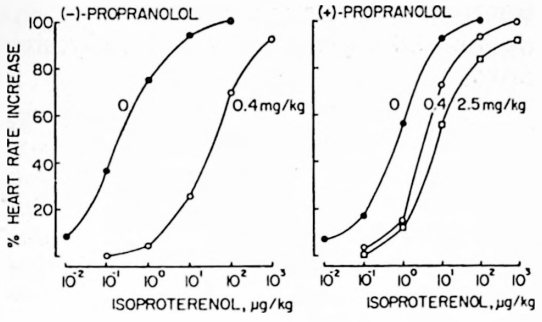

FIG. 2. Antagonism of (—)- and (+)-propranolol on the dose-dependent tachycardia produced by isoproterenol in anesthetized dogs.

at the cumulative dose of 10 mg/kg of (—)-propranolol.

(—)-Propranolol showed greater potency than the dextro isomer in blocking the isoproterenol-induced tachycardia, as demonstrated by the magnitude of the parallel displacement in the dose-response curves (fig. 2). The antagonism observed in the dose-related hypotension produced by isoproterenol varied with the isomer used: after (+)-propranolol the hypotension was either abolished or reduced, whereas after (—)-propranolol the depressor response obtained by low doses of isoproterenol was abolished, and that obtained by high doses was reversed into a pressor response (fig. 3).

OUABAIN-INDUCED CARDIAC ARRHYTHMIAS. The cumulative dose of ouabain needed for inducing ventricular tachycardia was 88.3 ± 16.1 (S.D.) μg/kg in the (+)-propranolol series, and 82.5 ± 10.0 μg/kg in the (—)-propranolol series (table I).

Six dogs were treated with (+)-propranolol. The first change observed in the cardiac rhythm was the conversion from the ventricular tachycardia into either a short-lasting sinus rhythm (4 dogs) or a nodal rhythm (2 dogs). The dose required was 2.3 ± 1.6 mg/kg. The temporary sinus rhythm obtained in the four dogs was consistently accompanied by a first degree A-V block (PR interval: 233 ± 51 msec) and aberrant conduction. These changes, however, were not permanently established. Out of the two animals with nodal rhythm, one developed lethal ventricular fibrillation; in the other dog, the nodal rhythm could not be modified by incresing doses of (+)-propranolol up to 5.8 mg/kg. In no animal the first period of sinus rhythm lasted for more than 5 min. In two animals the ventricular tachycardia reappeared and could not be reversed by subsequent doses of (+)-propranolol up to 10 mg/kg. In the other two dogs, increasing doses of the drug produced periods

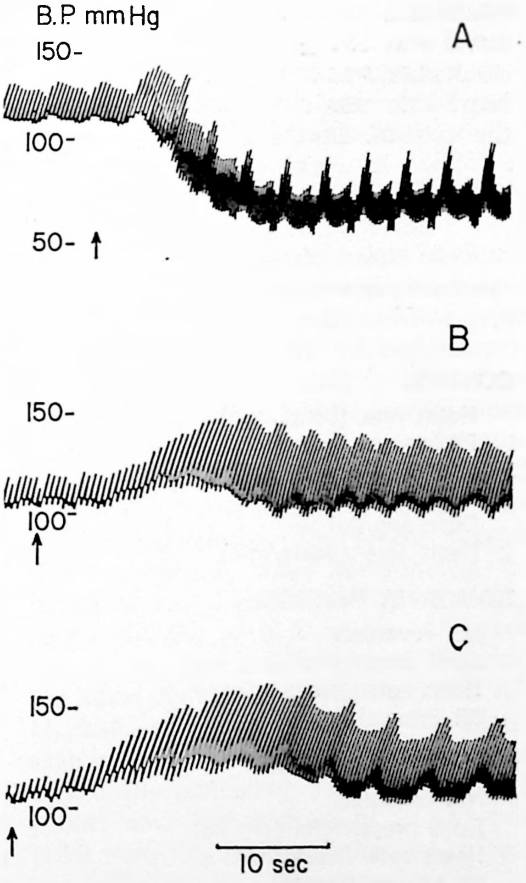

FIG. 3. Reversal of the depressor response to isoproterenol, 100 μg/kg (arrow), produced by (—)-propranolol in an anesthetized dog. A, control; B, after (—)-propranolol, 1 mg/kg; C, after (—)-propranolol, 2.5 mg/kg.

of nodal and sinus rhythm that alternated with ventricular tachycardia, until a permanent sinus rhythm was implanted. At this time the PR interval was 300 msec. The heart rate at the end of the experiment was not significantly different from that of the control period.

(—)-Propranolol reverted the ventricular tachycardia into sinus rhythm in 5 out of 6 dogs, the dose required being 1.2 ± 1.3 mg/kg. The PR interval was 142 ± 30 msec. However, this reversion was temporary, and ventricular tachycardia reappeared. Further doses of (—)-propranolol up to a total of 4.3 ± 2.0 mg/kg were needed in order for a permanent sinus rhythm to be established in the 5 animals. The PR interval was 154 ± 31 msec, and aberrant conduction was consistently observed. The heart rate was significantly slower than the control. In the sixth dog, terminal ventricular fibrillation appeared at the dose of 1.0 mg/kg of the antiarrhythmic drug.

Discussion

Our data confirm the findings of previous investigators (2, 7) that (—)-propranolol is a more potent beta blocker than (+)-propranolol. They further indicate that, contrary to the conclusions of HOWE and SHANKS (7), (—)-propranolol is more potent, on a molar basis, and more effective compound than (+)-propranolol in reversing ouabain-induced cardiac arrhythmias. In 3 out of 6 animals of the (—)-propranolol series a dose that produced substantial beta blockade, 0.4 mg/kg, was able to produce an initial but short-lasting reversion of the ventricular tachycardia into sinus rhythm. Maintained sinus rhythm

TABLE I

Effects of (—)- and (+)-propranolol on the ouabain-induced arrhythmias [a]

	(—)-propranolol	(+)-propranolol	p [b]
CONTROL			
Heart rate (beats/min)	188.6 ± 26.9	174.6 ± 16.3	n.s.
PR interval (msec)	85.0 ± 9.0	86.0 ± 11.0	n.s.
OUABAIN INTOXICATION			
Dose (μg/kg)	82.5 ± 10.0	88.3 ± 16.1	n.s.
Heart rate (beats/min)	213.0 ± 41.0	213.5 ± 25.5	n.s.
TEMPORARY REVERSAL			
No. reversals	5/6	4/6	
Dose propranolol (mg/kg)	1.2 ± 1.3	2.3 ± 1.6	< 0.01
Heart rate (beats/min)	167.8 ± 47.6	179.8 ± 47.0	n.s.
PR interval (msec)	142.0 ± 30.0	233.3 ± 51.7	< 0.02
PERMANENT REVERSAL			
No. reversals	5/6	2/6	
Dose propranolol (mg/kg)	4.3 ± 2.0	7.8 ± 1.2	< 0.01
Heart rate (beats/min)	128.6 ± 15.7 [c]	158.8 ± 12.5	< 0.02
PR interval (msec)	154.0 ± 31.1 [c]	285.3 ± 19.7 [c]	< 0.01

[a] Values are expressed as Mean ± S.D.
[b] Statistical evaluation of the difference between the two isomers.
[c] Significantly different from its own control value.

was obtained by higher doses in 5 out of 6 dogs. On the other hand, in 4 out of 6 dogs (+)-propranolol failed to correct permanently the arrhythmia even at doses which markedly affected intracardiac conduction, as revealed by the prolongation of the PR interval. The unreliability of the response to the dextro isomer, as observed in this study, is in contrast with the reports of BARRET and CULLUM (2) where (+)-propranolol was consistently effective in ouabain-intoxicated dogs. Our results, however, support the clinical evidence obtained in the treatment of cardiac arrhythmias with these two compounds (8).

The superiority of the levo over the dextro isomer as an antiarrhythmic drug must be confronted with their equipotent local-anesthetic and quinidine-like activities (2, 9). The correlation between local-anesthetic activity of the beta blocking agents and their ability to counteract ouabain-induced arrhythmias is still controversial. MJ-1999, which lacks local-anesthetic properties (9), showed some antiarrhythmic effect in ouabain-induced arrhythmias of anesthetized cats (14). On the other hand, (+)-propranolol reverted ouabain-induced ventricular tachycardia only at much higher dose levels than those required to increase significantly the ventricular conduction time and ventricular absolute refractory period (11). And finally, the reports on the antiarrhythmic effects of ICI-50172, a compound that selectively blocks the beta receptors in the heart but does not have local-anesthetic activity, are ambiguous (3, 5). It seems reasonable to suggest, therefore, that the beta adrenergic blockade plays some role in the reversion of these experimental arrhythmias.

Some features of the sympathetic activity appear to be selectively elevated during pentobarbital anesthesia. PRIANO et al. (13) have shown that the heart rate and total peripheral resistance were increased by pentobarbital about twice above the values observed in conscious dogs, whereas the stroke volume was substantially diminished. Heart rate figures in our animals were even higher than those reported in the above work. These changes probably reflect the increase in adrenergic activity needed to maintain the blood pressure at a normal level. This interpretation is substantiated by the reduction in heart rate produced by beta-blocking doses of (—)-propranolol in the control pentobarbitalized dogs. Therefore, it is possible that selective increase of sympathetic tone might sensitize the heart to the toxic action of the cardiac glycoside, and that, under these experimental conditions, the beta-blocking drugs might be effective to some extent through inhibition of the adrenergic influence. In this connection, it is interesting to point out that the antiarrhythmic dose of (—)-propranolol produced considerable beta-blockade in the control dogs. The presence of quinidine-like properties will potentiate the antiarrhythmic efficiency of the drug.

First degree atrioventricular blockade consistently accompanied the restoration of sinus rhythm in the ouabain-intoxicated dogs. The intensity of the PR interval prolongation was significantly greater than that produced either by propranolol alone in the non-intoxicated animals or by ouabain in the animals which were allowed to recover spontaneously from the ventricular tachycardia. The results suggest that propranolol, while antagonizing the action of the digitalis on the ventricles, acts additively with it on the AV node and/or the His bundle (4). At the time the sinus rhythm was restored, the AV blockade was more severe in the dextro than in the levo series, the difference being statistically significant. This was not unexpected since higher doses of (+)-propranolol were required, and the two isomers are equipotent local anesthetics.

Only (—)-propranolol was able to reverse the isoproterenol-induced hypotension into a pressor response. LEVY and AHLQUIST (10) found that dichloroisopro-

terenol converted the depressor phase of the response to ethylnorepinephrine into a pressor response, but not the depressor response to isoproterenol. Pronethalol and (±)-propranolol did produce reversal of the isoproterenol-induced hypotensión (1, 6). It has been proposed that this reversal is due to the unmasking of the weak alpha adrenergic activity of the beta agonist, since phenoxybenzamine reduces the pressor effect (6). In our experiments the reversal was consistently accompanied by an increase of cardiac frequency (fig. 3). It can be concluded, therefore, that the reversal was not exclusively accounted for by the unmasking of the alpha activity, but also by the residual action of isoproterenol on the incompletely blocked cardiac beta receptors, at a time when vasodilator beta receptors were completely blocked by propranolol.

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Summary

Beta-blockade potency and antiarrhythmic activity of the (+) and (—) isomers of propranolol were compared in anesthetized dogs. Dose-response curves for the tachycardia induced by isoproterenol were obtained. Cardiac arrhythmias (ventricular tachycardia) were induced by i.v. ouabain. (—)-Propranolol was more potent beta blocker than (+)-propranolol; only (—)-propranolol, at high doses, reversed the depressor response to isoproterenol. Beta-blocking doses of (—)-propranolol produced temporary reversion of the ventricular tachycardia, and high doses produced permanent reversion in 5 out of 6 dogs. On the other hand, (+)-propranolol succeeded only in 2 out of 6 dogs. AV blockade consistently accompanied the sinus rhythm restoration, but was more severe in the dextro isomer series. It is concluded that, in these experimental arrhythmias, beta-blockade seems to play an important role in determining the antiarrhythmic effectiveness of the drug, by inhibiting the sensitizing action of the adrenergic outflow on the ouabain-intoxicated heart.

References

1. ARIËNS, E. J., M. J. G. A. WAELEN, P. F. SONNEVILLE and A. M. SIMONIS: *Arzneim.-Forsch.*, **13**, 541, 1963.
2. BARRET, A. M. and V. A. CULLUM: *Br. J. Pharmacol.*, **34**, 43, 1968.
3. BARRET, A. M., A. F. CROWTHER, D. DUNLOP, R. G. SHANKS and L. H. SMITH: *Naunyn-Schmiedebergs Arch. exp. Path. Pharmak.*, **259**, 152, 1968.
4. DANATO, A. N., S. H. LAU, R. H. HELFANT, E. STEIN, W. D. BERKOWITZ and S. I. COHEN: *Circulation*, **39**, 287, 1969.
5. DUNLOP, D. and R. G. SHANKS: *Br. J. Pharmacol.*, **32**, 201, 1968.
6. FLACKE, J. W., P. F. OSGOOD and H. H. BENDIXEN: *J. Pharmacol. exp. Therap.*, **158**, 519, 1967.
7. HOWE, R. and R. G. SHANKS: *Nature* (Lond.), **210**, 1336, 1966.
8. HOWITT, G., M. HUSAINI, D. J. ROWLANDS, W. F. W. E. LOGAN, R. G. SHANKS and M. G. EVANS: *Am. Heart J.*, **76**, 736, 1968.
9. LEVY, J. V.: *Europ. J. Pharmacol.*, **2**, 250, 1968.
10. LEVY, B. and P. R. AHLQUIST: *J. Pharmacol. exp. Therap.*, **130**, 334, 1960.
11. LUCCHESI, B. R., L. S. WHITSIT and J. L. STICKNEY: *Ann. N. Y. Acad. Sci.*, **139**, 940, 1967.
12. PARMLEY, W. W. and E. BRAUNWALD: *J. Pharmacol. exp. Therap.*, **158**, 11, 1967.
13. PRIANO, L. L., D. L. TRABER and R. D. WILSON: *J. Pharmacol. exp. Therap.*, **165**, 126, 1969.
14. RAPER, C. and J. WALE: *Europ. J. Pharmacol.*, **4**, 1, 1968.