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Direct Myocardial Depressant Effects of Several β-Adrenergic Blocking Agents in the Unanesthetized Atherosclerotic Rabbit (40159)

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The property variously described as "direct membrane effects", "quinidinelike effects", "nonspecific membrane effects" and "direct myocardial depressant effects" is shared by many β-adrenergic blocking agents (1). Some of the antiarrhythmic effects of these compounds have been attributed to this property (2) as has the propensity to induce congestive heart failure in some clinical situations (3).

Nadolol has been reported to be five times more potent than propranolol in reversing isoproterenol-induced heart rate and electrocardiographic S-T segment changes in the unanesthetized, atherosclerotic rabbit (4). The present study was designed to compare several other β-adrenergic blocking agents in a similar manner. Since nadolol and propranolol completely reversed the effects of isoproterenol in the previous study we felt that their efficacy was solely attributable to β-adrenergic blocking effects. We therefore decided, for the present study, to determine beta-adrenergic blocking potency of the various agents by cumulative dose-response curves vs. the heart rate response to a single dose of isoproterenol and compare this with their direct myocardial depressant effects in these animals with a compromised coronary vasculature. The compounds chosen for study include four that have been reported to have direct myocardial depressant properties–propranolol, oxprenolol, alprenolol and pindolol (5), and three that reportedly do not, nadolol (6), timolol (7) and atenolol (8). With the exception of nadolol and propranolol, none of the other compounds has been previously studied in the atherosclerotic rabbit.

Materials and methods. Three-month old male New Zealand white rabbits were placed on a diet containing 2% cholesterol for 14–16 weeks.

β-adrenergic blockade experiments. For these studies the rabbits were lightly restrained on their backs and surface leads were placed on the spine and sternum for recording the electrocardiogram (ECG). Drugs were infused via the marginal ear vein. The heart-rate response to *l*-isoproterenol HCl (0.4 μg/kg) was measured twice at 20 min intervals and the average of these responses was taken as the mean control response. The dose selected caused approximately a 100 beat/min increase in heart rate. All β-adrenergic blocking drugs were given in cumulative half-log intervals over a 3-min period, starting with 1 μg/kg. Following each dose, the isoproterenol challenge was repeated and the percent inhibition of the control response was determined. Doses of β-blockers were increased at 20 min intervals until the heart rate response to isoproterenol was inhibited by approximately 90%. The highest dose tested was 3.1 mg/kg.

There were five rabbits each in all treatment groups. An additional group of five control rabbits was also studied to account for temporal changes in responses which might have occurred as a result of evolving a cumulative dose-response curve. These animals received equivalent volumes of saline only. Mean (± SEM) values for percent inhibition of isoproterenol-induced tachycardia were determined for each dose of β-blocker and the dose which inhibited the heart-rate response to isoproterenol by 50% (ID_{50}) was graphically estimated.

Myocardial depression experiments. For these studies a 14-gauge polyvinyl chloride catheter was implanted into the superior vena cava via the right external jugular vein under local anesthetic as previously described (4). At least 24 hr later, the unanesthetized ani-

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mals were lightly restrained and prepared for measurement of the ECG as above. The left carotid artery was exposed under local anesthesia (procaine HCl) and a micro-tip pressure transducer (Millar Instruments) was advanced into the left ventricle for measurement of ventricular pressure (LVP) and its first derivative (dP/dt). A bipolar pacing electrode was advanced into the right atrium via the indwelling catheter in the right jugular vein.

Right atrial pacing was instituted at a rate of 20–30 beats/min above the intrinsic heart rate. Infusion of a β-blocking agent (1 mg/kg/min) or saline was then begun at a rate of 0.2 cc/min via the marginal ear vein for a maximum of 100 min. Recordings were made one-half and one min into the infusion and then every minute for the first 30 min and then every 5 min thereafter for the balance of the study. Mean (± SEM) values for dP/dt during infusion of the β-blockers were determined and compared to those obtained during saline infusion. The mean dose which depressed dP/dt by 50% (Myocardial Depressant Dose$_{50}$; MD$_{50}$) was graphically estimated. The myocardial safety index (MD$_{50}$/ID$_{50}$) was then calculated for each drug.

Significant differences among drug effects were determined by Student's t test (9).

Results. The dose-response relationships with regard to inhibition of isoproterenol-induced tachycardia are plotted in Fig. 1 for those agents reported to have direct myocardial depressant effects and in Fig. 2 for those which are not. As indicated by the dotted lines, the maximum decrease in the heart-rate response to isoproterenol during saline control experiments was 20%. The most potent of the β-blocking agents was pindolol (ID$_{50}$ = 5 μg/kg) followed by nadolol (7 μg/kg), timolol (10 μg/kg), atenolol (24 μg/kg), oxprenolol (30 μg/kg), alprenolol (40 μg/kg), and propranolol (150 μg/kg). The differences among pindolol, nadolol and timolol were not significant ($P < 0.05$); likewise, among those of atenolol, oxprenolol or alprenolol.

The effects of the seven beta-adrenergic blocking agents on left ventricular dP/dt max are depicted in Figs. 3 and 4. The dotted lines indicate the maximal change in dP/dt observed in a group of saline-treated rabbits after 30 min (Fig. 3) or 100 min (Fig. 4) of infusion. Of the β-blockers tested those reported to possess membrane effects appear in Fig. 3. It is clear from Fig. 3 that the myocardial depressant effects of pindolol, oxprenolol and alprenolol, which cause a dose-dependent decrease in dP/dt max and death after 10 mg/kg, are similar. The decrease in dP/dt max seen after 1 and 2 mg/kg of propranolol is probably due to β blockade with direct depression occurring after the 5 mg/kg dose. Propranolol is approximately one-fifth as potent as the others in this regard but all animals died after 30 mg/kg.

As can be seen in Fig. 4, nadolol, atenolol and timolol all caused an initial depression of dP/dt max within the first minute of infusion, undoubtedly due to blockade of β-adrenergic stimulation. Only nadolol caused no further

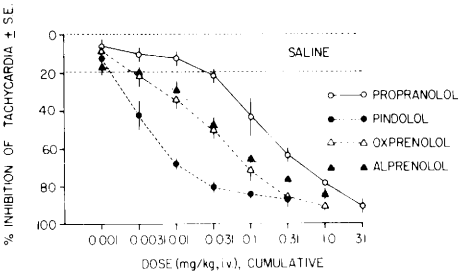

FIG. 1. Percent inhibition of the heart-rate response to isoproterenol by increasing doses of those β-adrenergic blocking agents with associated nonspecific membrane properties. The dotted lines in Fig. 1 and Fig. 2 indicate the maximum decrease in heart-rate responses to isoproterenol during saline control experiments. Pindolol was the most potent and propranolol the least potent drugs studied.

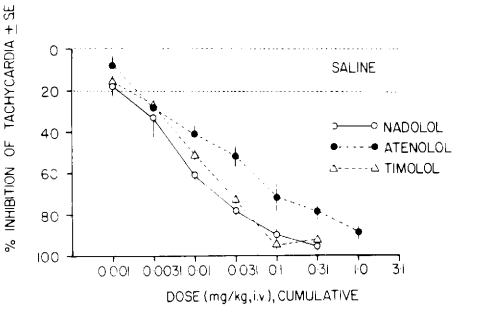

FIG. 2. Percent inhibition of the heart-rate response to isoproterenol by increasing doses of those β-adrenergic blocking agents without associated non-specific membrane properties. There is little difference in the dose-response relationships among these agents.

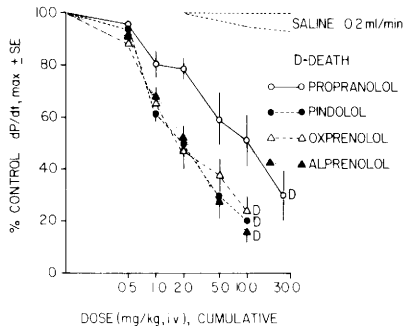

FIG. 3. Effect of infusion of propranolol, pindolol, oxprenolol, alprenolol (1.0 mg/kg/min) or saline on left ventricular dP/dt max. Inhibition of beta adrenergic stimulation during the first minutes of infusion caused a 20–35% decrease in dP/dt. Subsequent decrease is due to direct myocardial depression.

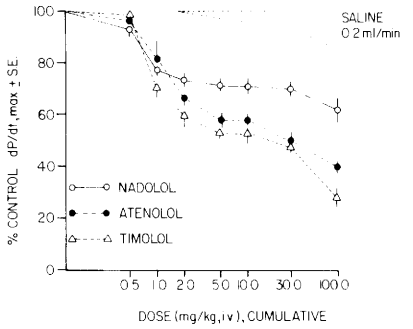

FIG. 4. Effect of infusion of nadolol, atenolol, timolol (1 mg/kg/min) or saline on left ventricular dP/dt max. The decrease in dP/dt due to β-adrenergic blockade is apparent at 1.0 mg/kg and amounts to 20–30%. Only nadolol caused no further myocardial depression.

significant depression of dP/dt even after a total intravenous dose of 100 mg/kg. Gradual additional decreases were obtained with infusion of atenolol and timolol, with their final values after a cumulative dose of 100 mg/kg being 40% and 28% of control, respectively, whereas that for nadolol was 62% of control. The estimated MD_{50} for timolol and atenolol is 20 and 40 mg/kg respectively, not significantly different, whereas that for nadolol is greater than 100 mg/kg. Timolol and atenolol caused a greater depression of dP/dt max ($P < 0.05$) than did nadolol at the 5 mg/kg dose and above.

The myocardial safety index for all seven compounds is shown in Table I. Those four agents reported to possess membrane effects have the lowest values with that of pindolol the highest due to its greater potency for beta-adrenergic blockade. Of the agents not reported to have membrane depressant properties, atenolol and timolol have similar myocardial safety index values whereas that for nadolol is at least seven times greater.

Discussion. Prichard (11) has recently reviewed the use of β-adrenergic receptor blocking agents in the treatment of angina pectoris. He concludes that all such agents that have been clinically tested are effective antianginal drugs. The compounds tested include representatives of all five groups classified by Fitzgerald (1) on the basis of associated properties such as selectivity, membrane stabilization and intrinsic sympathomimetic action. Thus, the antianginal efficacy of these agents is due primarily, if not solely, to their beta-adrenergic blocking properties. Presumably, the same mechanisms account for their efficacy in the treatment of acute myocardial infarction (12). Since patients with coronary artery disease are likely to have impaired cardiac function it would seem that the ideal β-adrenergic blocking agent for use in treating such patients is one with a high degree of potency and a lack of direct myocardial-depressant properties.

All seven β-adrenergic blocking agents studied effectively reduced the heart rate response to isoproterenol with a potency ratio of 30 between the most potent (pindolol) and the least potent (propranolol). The initial decrement in dP/dt during the infusion studies appears also to be attributable to β-adrenergic blocking activity. It was possible to graph-

TABLE I.[a]

	ID_{50}, μg/kg	MD_{50}, μg/kg	MD_{50}/ID_{50}
Nadolol	7	>100,000	>14,000
Timolol	10	20,000	2,000
Atenolol	24	40,000	1,700
Pindolol	5	2,000	400
Oxprenolol	30	<2,000	<70
Alprenolol	40	2,000	50
Propranolol	150	10,000	~70

[a] The inhibitory $dose_{50}$ (ID_{50}) vs. the heart-rate response to isoproterenol (0.4 μg/kg), the myocardial depressant $dose_{50}$ (MD_{50}), and the "myocardial safety index" (MD_{50}/ID_{50}) for all seven β-blockers studied. Clearly nadolol has the least propensity for causing direct myocardial depression.

ically estimate an MD_{50} for myocardial depression for each agent with the exception of nadolol which only reduced dP/dt to 62% of control following a total dose of 100 mg/kg. The myocardial safety index (Table I) indicates that nadolol has the highest safety margin. Timolol and atenolol have the next order of magnitude, whereas the other agents studied have considerably less cardiac safety. The clinical relevance of these results, particularly those obtained at many log multiples of the β-blocking dose is not clear at present, however, nadolol has the least propensity to cause direct myocardial depression in the atherosclerotic rabbit.

Summary. The beta-adrenergic blocking potency and myocardial depressant properties of seven β-adrenergic blocking agents were compared in unanesthetized atherosclerotic rabbits. The order of potency with regard to blockade of heart-rate responses to isoproterenol (0.4 μg/kg) was pindolol > nadolol > timolol > atenolol > oxprenolol > alprenolol > propranolol. Pindolol, oxprenolol and alprenolol caused the greatest depression of left ventricular dP/dt followed by propranolol, atenolol, timolol and nadolol. The "myocardial safety index" (MD_{50}/ID_{50}) was greatest for nadolol followed by timolol, atenolol, pindolol, propranolol, oxprenolol and alprenolol.

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