Competitive Antagonism Between Isoproterenol and a New Beta-Receptor Adrenergic Blocking Agent, Propranolol.* (30177)

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Although a number of studies have been made to elucidate the physiological and biochemical characteristics of the adrenergic receptors(1,2), the precise mechanism involved in the effector cells remains unknown(3,4). The advent of dichloroisoproterenol (DCI) has enabled several investigators to advance our present knowledge on the adrenergic mechanism through the beta-receptor blocking action of the drug(5-9). However, it has been shown that DCI possesses inherent sympathomimetic actions(6,8). Applying their observations to the concept of the drug actions postulated by Ariens and Simonis (4,10), Fleming and Hawkins(8) concluded that DCI is not a simple competitive blocking agent, and that the nature of the interaction between DCI and norepinephrine should be designated as competitive dualism. Very recently, Williams and Mayer(9) neither supported nor invalidated the hypothesis that DCI and norepinephrine compete for combining with the same receptor. Recently, a new compound, propranolol was synthesized and found to be a potent, "pure" beta-receptor blocking agent without any intrinsic sympathomimetic actions(11). The present study was undertaken to investigate the effects of different doses of isoproterenol on mean systemic arterial pressure and myocardial contractile force before and after geometrically increasing doses of propranolol in anesthetized dogs, and to ascertain the nature of the interactions of the two agents.

Methods. Dogs weighing between 18.5 and 21.0 kg were anesthetized with sodium pentobarbital (30 mg/kg). In all experiments the left hemithorax was opened under artificial respiration. The pericardium was incised and the heart suspended in a pericardial cradle. Sodium heparin solution (1.0 mg/kg) was given intravenously every half hour. Mean systemic arterial pressure was measured continuously with a Statham pressure transducer (P23AA) connected to a catheter placed in the left subclavian artery through the left internal mammary artery. Myocardial contractile force was measured continuously with a Walton-Brodie strain gauge arch(12,13) which was sutured directly to the right ventricular muscle. Both parameters were recorded continuously with an Electronics for Medicine recorder (Model DR8). Geometrically increasing doses (0.004-312.5 μg/kg) of isoproterenol HCl were administered intravenously every 5-10 minutes before and 10 minutes after the intravenous injection of geometrically increasing (cumulative) doses (50-6250 μg/kg) of propranolol to dogs.

Results. The results of the effects of isoproterenol on mean arterial pressure and myocardial contractile force before and after administration of propranolol were consistent in all 8 dogs. Tracings from a representative experiment are illustrated in Fig. 1, and the average effect of graded doses of isoproterenol on myocardial contractile force is summarized in Fig. 2. Fig. 1 shows that, during a control period, isoproterenol decreases systemic arterial pressure and increases myocardial contractile force essentially in proportion to the doses given. With administration of increasing doses of propranolol, the effects of given doses of isoproterenol on both parameters decreased progressively. However, the larger doses of isoproterenol surmounted the blocking effect of propranolol on myocardial contractile force. On the other hand, the effect of isoproterenol on systemic arterial pressure became biphasic, an initial, rapid rise being followed by a slower decrease. This increase in systemic arterial pressure became extremely marked with larger doses of isoproterenol after larger doses of propranolol were given (Fig. 1). Fig. 2 shows that each dose-response curve of isoproterenol on myocardial contractile force is shifted progressively to the right, essentially

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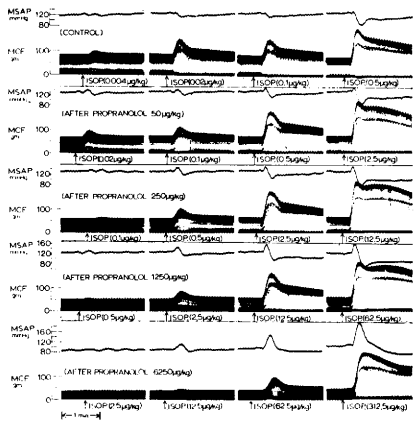

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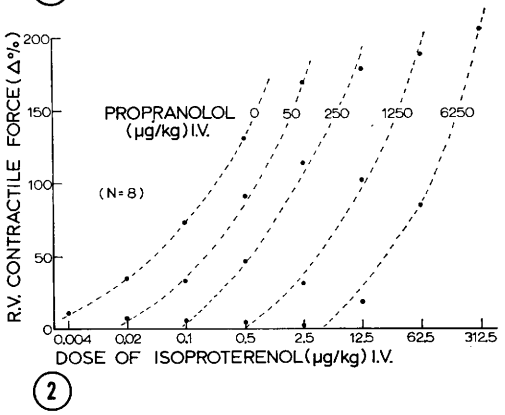

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FIG. 1. Effects of I.V. administration of geometrically increasing doses of isoproterenol on mean systemic arterial pressure (MSAP) and myocardial contractile force (MCF) before and after I.V. injections of geometrically increasing (cumulative) doses of propranolol in a dog.

FIG. 2. Summary of average effect of administration of geometrically increasing doses of isoproterenol on myocardial contractile force before and after administration of geometrically increasing (cumulative) doses of propranolol in 8 dogs.

in parallel with each other, as the dose of propranolol increased geometrically.

Discussion. From the present study, it is evident that the effects of given doses of isoproterenol on systemic arterial pressure and myocardial contractile force were inhibited or completely blocked by progressively increasing doses of propranolol. The larger doses of isoproterenol were always found to surmount the blocking effect of propranolol on myocardial contractile force. The dose-response curves of isoproterenol were shifted progressively to the right, essentially parallel with each other as the dose of propranolol increased geometrically (Fig. 2). This family of dose-response curves appears to satisfy the concept of competitive antagonism between 2 pharmacological agents, which has been advocated by Ariens and Simonis (4,10). Hence, one could conclude that competitive antagonism does exist between isoproterenol and propranolol. In addition, the present study revealed that the larger doses of isoproterenol cause a biphasic response on systemic arterial pressure, an initial increase being followed by a decrease when the larger doses of propranolol were given previously. As demonstrated in the last segment of the tracing (Fig. 1), systemic arterial pressure increased markedly shortly after administration of an extremely large dose of isoproterenol. This observation seems to prove that isoproterenol possesses a vasoconstrictor (alpha-receptor stimulator) property which is almost always masked completely by its more intense vasodilator (beta-receptor stimulator) property before administration of propranolol.

Recently, in this laboratory, further studies have been made on the present problem in vagotomized, open chest dogs as well as in different preparations such as the dog hindlimb preparation(14) and the isolated atrium preparation(15). It was found that qualitatively similar competitive antagonism also exists between isoproterenol and propranolol for adrenergic beta-receptors in the myocardium and vascular smooth muscles. In addition, after the large doses of propranolol, the transient vasoconstricting (alpha-receptor stimulating) effect of isoproterenol was also demonstrated clearly in the dog hindlimb preparation in which arterial blood was perfused constantly by means of a Sigmamotor pump.

Summary. The effects of graded doses of isoproterenol on mean systemic arterial pressure and myocardial contractile force were studied in anesthetized dogs before and after administration of graded doses of a new beta-receptor blocking agent, propranolol. It was found that, with geometrically increasing doses of propranolol, the effects of given doses of isoproterenol on systemic arterial pressure and myocardial contractile force decreased progressively. However, the larger doses of

isoproterenol surmounted the blocking effect of propranolol on myocardial contractile force. Dose-response curves of isoproterenol after graded doses of propranolol indicate the existence of competitive antagonism between isoproterenol and propranolol. In addition, after administration of propranolol, the effect of isoproterenol on systemic arterial pressure was found to become biphasic, an initial increase being followed by a decrease. Hence, it is postulated that isoprotenerol possesses a vasoconstrictor (alpha-receptor stimulator) property which is usually hidden by a more marked vasodilator (beta-receptor stimulator) property of the drug.

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A Transmitter for Telemetering Electrophysiological Data. (30178)

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In the study of normal animals and of animal toxicoses and disease processes it is often desirable to obtain information concerning the state of a body system over an extended period. Radio telemetry offers the advantage of being able to transmit electrophysiological data from an animal without the encumbrance of attached wires. Devices have been proposed, but are designed for a specific usage or are limited in frequency response and signal to noise ratio(2,3,4).

The objective of this study was to design a radio frequency transmitter that could be attached to an animal without interfering with the animal's behavior in its normal environment and also versatile enough to be used on an animal as small as a pigeon or as large as a cow. In the authors' opinion, a simplified practical device for use in physiological measurements was needed. The design objective was faithful transmission of electroencephalograms, electrocardiograms, and respiratory rates. Special emphasis was placed on size, weight, frequency response, input impedance, signal to noise ratio, stability and battery life. This paper reports the design of an instrument which meets most of the above objectives.

Description. The circuitry of the transmitter is shown (Fig. 1). It consists of a preamplifier and a high frequency oscillator. The preamplifier, consisting of transistors Q1 and Q2, offers a high input impedance of 500,000 ohms and a low output impedance with a voltage gain of approximately four. The oscillator section contains transistor Q3,