Influence of Sympathomimetic Pressor Drugs on Arrhythmias Caused by Multiple Stimuli

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A technic of administering successive stimuli to the heart at various ectopic foci was devised. Under normal circumstances the heart had sufficient power of integration to resist disorganization of its action by these multiple stimuli. Methoxamine, mephentermine and metaraminol had less tendency to increase vulnerability to fibrillation than did levarterenol under these conditions of stress. A new compound (Lilly #20522) blocked for a time the arrhythmia-producing action of levarterenol.

In a recent communication, this laboratory reported on the propensity of certain sympathomimetic pressor drugs to affect cardiac irritability, to produce ectopic pacemaker action and spontaneous extrasystoles, as well as to create a condition productive of abnormal or multiple responses to single ventricular test stimuli. It was thought desirable to study further this disorganizing action which characterized certain pressor agents more than others.

There have been many previous reports on different aspects of this theme. Numerous studies have shown the arrhythmia-producing properties of the combination of vasoconstrictors and anesthetics. Others have revealed the frequency of ectopic rhythms in dogs after coronary ligation coincident with the administration of various agents. Therefore our purpose was to devise a new technic and one which would provide a well-controlled means of studying the arrhythmia-producing properties of pressor drugs and the ability of certain blocking agents to decrease these effects. In other words, we desired to produce a situation which conceivably would not be too far removed from clinical realities and stressful enough to ventricular organization to produce abnormalities of rhythm in the presence of exciting drugs but not in their absence.

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The method employed to render the heart more than normally vulnerable to the action of arrhythmia-producing drugs was that of creating multiple foci of beat origin. The project to be described, therefore, can also be considered a testing of the power of the heart to fuse the action of multiple "pacemakers" under controlled conditions and when affected by pressor drugs.

Methods

Mongrel dogs varying between 11 and 16 Kg. in weight were anesthetized with pentobarbital (30 to 40 mg./Kg. intravenously) and a midline sternal incision was made to expose the heart. Artificial respiration was employed throughout the experiments. The vagi were cut in the neck, the sinoatrial node was crushed, and the heart driven through an auricular electrode by stimuli applied at the rate of 200 or 172 per minute. Stimulating electrodes were placed on both the right and left ventricles, as was a single bipolar pickup electrode on the right ventricle for oscilloscopic recording (fig. 1). Unipolar extremity lead electrocardiograms were also recorded on a two channel electrocardiograph.

A strength interval curve was first obtained for the right ventricle. When the absolute refractory period was thus ascertained, the pulse from the right ventricular stimulator was so adjusted as to fall 20 msec. after the beginning of the recovery period of the normal ventricular beat. This extra stimulus was slightly supra-threshold in strength and delivered every twelfth beat. Within the recovery period of the extrasystole thus induced, the left ventricle was stimulated at intervals of 10 to 20 msec. from about the time of full recovery to the border of the extrasystole's absolute refractory period with 3 msec. rectangular stimulus pulses of 6, 15, and 30 ma. intensity. In spite of this exceedingly stressful situation created by the arrival of two successive stimuli to the ventricles in varying
Figs. 1. Diagram of heart illustrating placement of the auricular drive, the right \( (S_1) \) and left \( (S_2) \) stimulatory electrodes, and the electrogram pickup electrode.

The drugs,\(^*\) levaterenol, methoxamine, mephentermine, epinephrine, and metaraminol were administered by intravenous infusion, the dosage at first being determined by the rate necessary to raise the blood pressure 30 to 50 mm. Hg. Later, higher doses were also tested. In addition, two blocking agents were used in conjunction with levaterenol, namely, phentolamine, and l-(3', 4'-dichlorophenyl) -2-isopropylaminoethanol hydrochloride, hereafter referred to as #20522. The details of the individual doses will be discussed under the results obtained with each drug.

**RESULTS**

Our observations were directed at the production of abnormal responses resulting from the above-described double stimulation procedure. These abnormal responses were usually one or more additional ectopic extrasystoles following the two normally caused by the stimuli, but sometimes a ventricular tachycardia or fibrillation occurred after drug administration. Such activity was correlated with dosage and any tachyphylactic tendencies were noted.

As expected, levaterenol administered to 5 animals was most consistent in producing arrhythmias under these conditions. Thus in 1 dog control testing with the above-described technique produced no extra responses other than the specific ones to the test stimuli. When a solution of 2.5 \( \mu \)g./ml. of levaterenol was administered at the rate of 7.75 \( \mu \)g./min. multiple responses were observed when the strength of the second stimulus was 15 ma. This dosage raised the blood pressure from 80 mm. Hg to 120 to 130 mm. Hg. When the dose was increased to 17.2 \( \mu \)g./min. there were consistent multiple responses through the entire time range of stimulation; in other words, through the entire recovery period following stimulus 1 and with all three strengths of the second stimulus, 6, 15, and 30 ma. As soon as the rate of infusion was dropped to the original level, the extra responses were unobtainable, but returned when the dosage rate was again increased.

In another typical levaterenol experiment during the control test itself there occurred a single multiple response at one point of the cycle. When the infusion was given at the rate of 12 \( \mu \)g./min. there were multiple responses evoked at every point in the recovery period of stimulus one. These trains of extrasystoles almost completely disappeared when the rate of drug infusion was slowed to 5.25 \( \mu \)g./min. The initial blood pressure, which was 70 mm. Hg, rose to 170 mm. Hg and then fell to 110 mm. Hg when the lower rate of infusion was again instituted. In this particular animal, the whole phenomenon was repeated twice. Figure 2 is a typical illustration of such results and includes an example of ventricular fibrillation.

Of the drugs tested, none produced as much rhythmic disturbance as did levaterenol. Thus in one methoxamine experiment of which three were done, with an infusion rate of 28 \( \mu \)g./min. which increased the blood pressure...
from 110 to 170 mm. Hg, there were no multiples at all under the conditions maintaining. In another methoxamine experiment, after this drug failed to produce any arrhythmic disturbances beyond those normal to the control stimulations, levarterenol was given to the same animal. At a rate of levarterenol infusion of 12.75 μg./min., there were numerous multiple responses to the two stimuli, and at the higher rate of 20.5 μg./min., ventricular fibrillation ensued.

Mephentermine, used in 6 dogs in doses varying between 1.25 to 3.0 mg./min., was slightly inconsistent in its effects but these could be summed up generally as follows: A moderate increase in irritability was produced for a short period of time (10 to 20 min.) during which multiple responses were obtainable, but thereafter they were not again observed even following a tremendous increase in the dose rate. Again, to prove that the later inability to produce multiple responses with this drug was not due to a peculiarity of the animal or to some drug-induced inhibition, levarterenol was subsequently administered and produced its expected effects.

The results with metaraminol were very interesting. In the first experiment, we were unfamiliar with the proper dosage and administered a solution of 50 mg./L. and started with a rate of 0.270 mg./min. This raised the blood pressure from 80 to 200 mm. Hg and caused a tremendous degree of ventricular excitation and a consequent ventricular tachycardia. The rate of drug inflow was drastically reduced and eventually the ventricular pacemaker action disappeared, but even a moderate dose rate of 0.115 mg./min. produced many multiple responses even with one ventricular stimulus alone. The dual extra stimuli could not be tolerated.

However, in the subsequent four experiments a concentration of 30 mg./L. was used and a lowered initial rate of infusion. Thus in two experiments a rate of 0.075 mg./min. raised the BP from 80 to 150 mm. Hg, and in a third, a rate of 0.063 mg./min. raised the BP from 60 to 120 mm. Hg. In all these instances, the double stimulation procedure produced either no multiples at all or extremely rare ones. Furthermore, when the dose rate was subsequently increased in these experiments to such levels as 0.270 mg./min. or even to 0.330 mg./min. at the same time driving the pressure as high as 200 mm. Hg, there was no increase in the propensity to produce arrhythmias. After proving to ourselves the innocuousness of this drug when the initial infusion was started conservatively, we repeated the first experiment of too large an initial dose, and again observed the results seen at first: tremendous excitation with the production of ventricular pacemakers. We might add that this drug shortens A-V conduction time and also the absolute refractory period. Effects on these characteristics by the other drugs have been reported previously.1

Additional experiments were conducted to determine the possible ability of 20522 to inhibit the arrhythmias produced by levar-
To this end we used varying doses and also two procedures, namely, administration of $20522$ after the levarterenol infusion was in progress, and administration of $20522$ before infusion of levarterenol. When $2 \text{ mg.} / \text{Kg.}$ or less were used in 3 dogs, there was no protective effect whatsoever. However, an additional 7 dogs were treated with doses of $4 \text{ mg.} / \text{Kg.}$ or higher. Of these, 5 were given $20522$ after the levarterenol infusion had been started, and 2 were given the drug before any levarterenol was administered.

Discussing first the latter group, both animals were given $4 \text{ mg.} / \text{Kg.}$ (in a total of 2.2 ml. of water). In the first, the arterial pressure dropped from 100 to 50 mm. Hg but returned to 60 mm. Hg before the levarterenol infusion was begun. This required about 20 minutes. In the second, arterial pressure fell from 110 to 85 mm. Hg. A high dosage of levarterenol was given; rates of $17.2 \mu g. / \text{min.}$ up to $24.5 \mu g. / \text{min.}$ which raised the blood pressure to 180 mm. Hg. In the first animal there was excellent protection, and only a rare multiple extrasystole occurred in response to the multiple stimuli for two and a half hours. After this period, however, the inhibition wore off and multiple extrasystoles were observed in the accustomed frequency. Eventually ventricular fibrillation occurred. In the second dog, the protection was excellent for over three hours, but finally the multiple responses to the paired stimuli did appear with a high dosage rate of levarterenol. Protection did not last indefinitely.

In the 5 experiments in which $20522$ was given after the levarterenol infusion was already in progress and after control runs revealed the multiple responses occurring after the double stimuli, there was one animal in which successive doses of 4, 4, and 8 \text{ mg.} / \text{Kg.} afforded no protection, and another in which a dose of 8 \text{ mg.} / \text{Kg.} did inhibit completely the multiple responses but shortly thereafter produced a complete heart block from which the animal did not recover. In the other three animals protection was observed. In one, a dose of 4 \text{ mg.} / \text{Kg.} showed an excellent inhibitory effect for one and one half hours. This protective action was associated with no other deleterious effect, though the arterial pressure did drop temporarily from 110 to 80 mm. Hg. The second also was given a dose of 4 \text{ mg.} / \text{Kg.} and the third 6 \text{ mg.} / \text{Kg.} In both inhibition of the arrhythmia-producing propensity of levarterenol occurred, and in the latter instance complete protection lasted for 45 minutes and partial protection for an additional hour. Again $20522$ produced a momentary (15 to 20 minutes) drop in the arterial pressure, which was frequently followed by a rise to a level even higher than the original. Also there was a frequent transitory increase in A-V conduction time. This again was in contrast to the effects of levarterenol.

Finally, the same procedures were attempted with phentolamine as for $20522$. The purpose, of course, was to ascertain if this adrenergic blocking agent could inhibit the levarterenol effects on the heart. In the first of these experiments, after a rate of levarterenol injection had been established sufficient to produce the accustomed multiple responses to the two successive stimuli, 2 \text{ mg.} / \text{Kg.} of phentolamine was slowly infused. The arterial pressure dropped from 110 mm. Hg to a level of 40 mm. Hg from which it did not significantly recover for about two hours. During this period there was substantial though not complete protection, lasting over one and one half hours, after which the arterial pressure rose and the multiple responses to testing stimuli returned. In the next experiment, after the levarterenol infusion had begun, the blood pressure had risen to 160 mm. Hg and numerous multiple responses had been observed, a dose of 1 \text{ mg.} / \text{Kg.} of phentolamine was infused. This had a tremendous hypotensive effect but it also produced good protection abolishing the multiple responses for 20 minutes. They returned, however, as the blood pressure started to rise. In the next animal, 1 \text{ mg.} / \text{Kg.} of phentolamine was administered before any levarterenol was given. This dose lowered the arterial pressure from 85 to 40 mm. Hg. This produced moderate protection against the arrhythmia-producing effects of the levarterenol which was then
given. This protection gradually lessened and one hour later, with the arterial pressure at 90 mm. Hg, levarterenol infusion produced not only many multiples but ultimately ventricular fibrillation. After the heart had been defibrillated, an additional 1 mg./Kg. of phentolamine was given but no protective effect whatsoever resulted. Finally, even though the protective action of 1 mg. of this drug had been neither marked nor prolonged, it was felt that a dose small enough to avoid a significant hypotensive effect should be tried to test the inhibitory ability of the drug un-associated with a lowering of arterial pressure. Therefore 0.25 mg./Kg. was injected. Even this small dose produced a drop in blood pressure of 30 mm. (from 90 to 60). Levarterenol was infused at the usual rate and the testing begun. Multiple extrasystoles were elicited through the entire cycle, indicating that no protection had been established with this dose.

DISCUSSION

Our purpose as stated in the introduction was achieved, namely a specific technic was devised for studying the arrhythmia-producing propensities of certain drugs, in this case the vasopressors. The theory that fibrillation results from establishment of multiple ectopic foci of beat origin has strong support, but it has not been determined how many such ectopic foci are necessary and what their sequence of action must be to produce disorganization of heart action or fibrillation. This technic of studying the effects of multiple stimuli has shown that the heart possesses great ability to fuse the impulses coming from at least a number of sites within the ventricles. In these experiments, at times impulses were arriving through the normal conducting system from the auricular pacemaker, from an origin both at an anode and cathode on the right ventricular surface near its base and from an anode and cathode placed near the apex of the left ventricle. No study was made of the significance of ventricular electrode placements, but the sequence of impulse origin from these sources was important. Under control conditions, despite the stress thus placed on the integrative powers of the myocardium, multiple firing and/or fibrillation did not occur. Injection of the various vasopressor drugs in varying concentrations added different degrees of stress for which the myocardium could not always compensate and arrhythmias resulted.

In view of our previous studies it was not surprising to find that with such procedures levarterenol (as well as epinephrine which was not specifically mentioned in the preceding section) gave evidence of an ability to disorganize cardiac rhythm when coupled with the application of successive multiple stimuli. Furthermore, it was also consistent with our previous studies as well as those reported by others that methoxamine raised arterial pressure without producing disorganization and that mephentermine had very little arrhythmia-producing action even under these circumstances. The newer drug, metamizanol, in spite of its excitatory powers when used in an inordinately large dosage, seemed, at least in these experiments, to be the drug of choice, when one considers the absence of arrhythmia production when the compound was given in proper dosage, its prolonged ability to maintain blood pressure, and the final fact that it does not prolong A-V conduction. In both of these last characteristics it exhibited a superiority over methoxamine and of course it was also superior to levarterenol with respect to the first category of action. Incidentally, two clinical reports indicate further advantages, such as slow decline in effect when administration is stopped and a lack of local tissue reaction.

Very recently, the new product Lilly 20522 has been synthesized, and reported to have the property of blocking certain effects of sympathomimetic amines on the smooth muscle of bronchi, uterus, and intestines. This phenomenon had been noted by other observers in the case of certain sympathomimetic amines, such as ephedrine, but all of these drugs also have an excitatory action of their own. It has been observed that 20522 in the dose used does not exhibit such an excitatory action, and thus is unique in its abil-
ity to combine with the adrenergic inhibitory receptor substance presumably located in such smooth muscles as mentioned above.

According to a current hypothesis, of which the last statement is a part, there also exist adrenergic excitatory receptor substances and these would normally be found, for example, in certain blood vessels which contract when activated by sympathomimetic amines. Moran and Perkins studied the effect of $20522 on the inotropic action of compounds on the heart and concluded that this drug produces a relatively specific blockade of positive sympathetic cardiac inotropic effects. They therefore suggest the hypothesis that the myocardial receptors are functionally homologous to the receptors in the smooth muscles of bronchi, uterus, etc., termed "adrenergic inhibitory receptors of smooth muscle" insofar as the action of this drug is concerned.

H. H. Swain of the University of Michigan in a personal communication to I. H. Slater of the Lilly Company noted the ability of $20522 to block ventricular fibrillation produced by various drugs in combination with epinephrine, such as methyl chloroform. If $20522 is able to block cardiac effects of sympathomimetic amines by the means postulated, then conversely, an agent which inhibits the adrenergic excitatory responses but does not block these "adrenergic inhibitory receptors" should not act to prevent the arrhythmia-producing actions of these vasoconstrictors. Actually, there is some evidence that these peripheral blocking agents which affect adrenergic excitatory responses do inhibit to some extent the arrhythmia-producing propensities resulting from the combination of anesthetics and sympathomimetic amines. In our experiments phentolamine did produce a moderate inhibitory effect, but only in doses which profoundly lowered the arterial pressure. On the other hand, $20522 produced a more definite and long-lasting protection with dosages that were safe as far as arterial pressure effects were concerned. These experiments are therefore consistent with the hypotheses discussed above, although they do not constitute proof of its complete validity. To produce additional support it would be necessary to study the basic pharmacologic actions of this drug on the heart in order to rule out the possibility that it has an antifibrillatory action unrelated to its adrenergic blocking property. Nevertheless our results though they require verification and expansion, are of interest from the point of view not only of pharmacology and physiology but also of clinical medicine which would benefit from the discovery of a vasopressor drug with no undesirable cardiac actions or of a drug which would protect the heart from the undesired effects of useful vasopressor agents.

**Summary**

A technic for studying the arrhythmia-producing properties of sympathomimetic drugs has been described. This method could also be considered to test the power of the heart to resist the disorganizing action of multiple "pacemakers" under control conditions and when affected by sympathomimetic amines. The experiments reported illustrate the varying degrees to which these drugs affect vulnerability to fibrillation and the fibrillatory process. The possibility that blockade of receptors might protect the heart against undesirable action of sympathomimetics was considered and in this connection the action of a new drug (Lilly $20522) reported to block adrenergic inhibitory receptor substance was tested.

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**Summary in Interlingua**

Es describite un technica pro le studio del proprietates pro-arrhythmiae in drogas sympathomimetic. Le metodo pote etiam esse considerate como testante le resistencia del corde contra le effecto disorganisatorii de multiple cardiocentiores sub conditiones de controlo e quando affice per aminas sympathomimetic. Le experimentos reportate illustra le varie grados a que iste drogas influenta le vulnerabilitate per fibrillation e le processo fibrillatorii. Esseva considerate le possibilitate que
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un blocada de receptores protege le corde contra le action adverse de agentes sympatho-
imetic. In iste connexion, le action de un nove droga (Lilly #20522) esseva testate con respecto a su reportate capacitate de bloquear substantia receptori de inhibition adrenergic.

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