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Prolonged Catecholamine-Dependent Cardioaccelerator Action of Bretylium (32896)

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Adrenomimetic manifestations following the administration of bretylium have been demonstrated in several species of animals and in different types of experimental conditions. These studies have been reviewed by Boura and Green (1), and by Holtz and Palm (2). It is generally agreed that the adrenomimetic effect of bretylium is due to the release of norepinephrine from adrenergic nerve endings because it occurs in isolated tissues (3) and adrenalectomized animals (4); it does not occur in tissues depleted of catecholamines by reserpine, and it may reappear if the reserpinized preparation is treated with norepinephrine (3,5–7). Also the adrenomimetic responses following bretylium can be blocked by appropriate adrenergic blocking agents (5,7). The duration of adrenomimetic effect following injection of bretylium is said to be 20–30 min, as judged from the change in blood pressure, heart rate, and the contractility of the heart (5,8). The results obtained in these studies of effects on heart rate in dogs with baroceptor reflexes inactivated indicate that adrenomimetic effects continue considerably longer than has been reported previously.

Method. Dogs weighing 9–15 kg were premedicated with morphine (3 mg/kg) and anesthetized by intravenous injection of α-chloralose (100 mg/kg) or pentobarbital (20 mg/kg). In order to suppress the influences of buffering reflexes, tetraethylammonium chloride (TEAC) was administered in doses of 20–25 mg/kg intravenously and, at the same time, an additional 40–50 mg/kg intramuscularly. The TEAC produced an initial rise in the heart rate, and 40–50 min later the heart rate became stable. Then bretylium was injected. The heart rate was determined from lead II of the electrocardiogram. The number of cardiac cycles/10-sec period, including fractions, was counted and the rate expressed as beats/min. Blood pressure was measured by a Statham pressure transducer connected by polyethylene tubing to a needle in the femoral artery. All recordings were made on a Gilson polygraph.

Vagotomized spinal dogs were prepared by transecting the spinal cord at the level of C_2 and cutting vagi at the middle cervical level. Respiration was maintained by a Harvard respirator. After the heart rate and blood pressure became stable bretylium was injected.

For the studies of urinary catecholamine output urine was collected from female dogs by catheterization. The experiment was divided into four periods. The first period was the 45-min period after TEAC administration and before bretylium injection. The second period was the first 20 min after bretylium injection and the third and fourth periods were from 20–80 and from 80–180 min, respectively, after bretylium injection. Epinephrine and norepinephrine in urine were determined by the method of Anton and Sayre (9) using Aminco spectrophosphorimeter–fluorometer.

Results. Bretylium tosylate, in doses of 10

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mg/kg intravenously, was administered to dogs which had received TEAC. The heart rate before bretylium was 93.7 ± 3.7 (av ± SE) beats/min in the nine dogs studied. After injection of bretylium there was an immediate rise in the heart rate which was often accompanied by ventricular ectopic beats or ventricular tachycardia. The maximum increase in heart rate occurred within 5 min, then it fell rather rapidly initially, then decreased gradually. In the nine dogs the heart rate was 145.7 ± 6.0 beats/min and 136.6 ± 6.9 at 120 and 180 min, respectively, after bretylium injection (Fig. 1). In seven

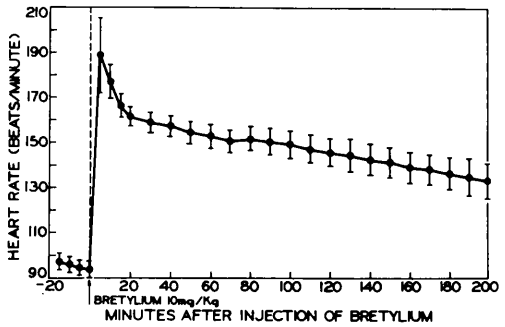

FIG. 1. Effect of bretylium on heart rate in dogs under the influence of tetraethylammonium chloride. Average and standard error of the heart rate in experiments on nine dogs.

dogs in which the blood pressure was measured the systolic pressure was 28.5 ± 7.5% higher and the diastolic pressure was 40.0 ± 9.5% higher than the control at 120 min after bretylium injection ($0.01 > p > 0.001$). At 180 min the systolic pressure was 11.6 ± 6.1% higher and the diastolic pressure was 19.8 ± 6.8% higher than the control. The former was not significant statistically; the p value for the latter was between 0.05 and 0.02.

In order to determine whether the sustained elevation in heart rate after bretylium was catecholamine-dependent the effect of the beta adrenergic receptor-blocking agent, propranolol, was studied. Propranolol in doses of 1–2 mg/kg, injected intravenously in six dogs, at 82, 83, 90, 171, 174, and 203 min, respectively, after bretylium injection caused the heart rate to decrease within 5 min from the elevated level to within 10 beats/min of the control level.

Two vagotomized spinal dogs were studied to determine whether the sustained elevation in heart rate is due to effects of TEAC other than its ganglion-suppressing action. Bretylium produced the prolonged elevation in heart rate in both animals similar to that which was produced in ganglioplegic dogs. In one of these propranolol was given intravenously, and it caused the heart rate to return to the control level within 4 min (Fig. 2).

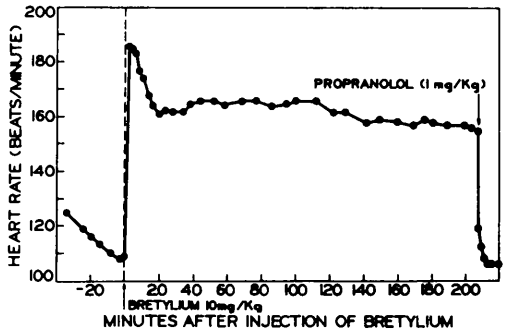

FIG. 2. Effect of bretylium and propranolol on the heart rate of a vagotomized spinal dog.

Effects of bretylium on the urinary catecholamine output were studied in four dogs which had received TEAC. During the period after TEAC administration and before the bretylium injection the urinary norepinephrine and epinephrine outputs were 3.01 ± 1.11 and 5.84 ± 1.15 mμg/min, respectively. Immediately after bretylium injection the norepinephrine output (26.81 ± 5.44 mμg/min) was about nine times as high as before, whereas the epinephrine output (3.95 ± 2.75 mμg/min) was not significantly changed. In the period 20–80 min after bretylium injection, the urinary norepinephrine and epinephrine outputs were 3.79 ± 0.38 and 0.98 ± 0.19 mμg/min, respectively, which was not significantly different from the period before the bretylium injection. In the period 80–180 min after the bretylium injection the norepinephrine output was 4.41 ± 1.60 mμg/min and the epinephrine 0.22 ± 0.02 mμg/min. The latter was significantly lower than the period before the bretylium injection ($0.02 > p > 0.01$). The urinary catecholamine output up to 228 min after TEAC injection in a dog which had not received bretylium was measured, and it was found that the urinary nor-

epinephrine output remained low throughout the seven collection periods. It ranged from 1.76–2.62 mμg/min with an average of 2.12 mμg/min. The urinary epinephrine output during the first 18 min after TEAC injections was 3.65 mμg/min and thereafter the outputs were lower (range from 0.16–1.53 mμg/min, with an average of 0.82 mμg/min).

Discussion. Boura and Green (4) suggested that the adrenomimetic effect which occurs immediately following the injection of bretylium is due to the release of catecholamines from adrenergic tissue. This has been confirmed in dogs (8), spinal cats (5), rats (6), and men *in vivo,* and also in isolated atria of rats (7), guinea pigs, and cats (3), heart–lung preparation of dogs (10), rabbit aortic strips (3), and in spleen pretreated with tritium-labeled norepinephrine (11). It was indicated again in the present studies by the rise in blood pressure and heart rate which occurred following administration of bretylium to ganglioplegic dogs and to vagotomized spinal dogs, by the fact that the elevated heart rate could be reduced immediately to the control level by propranolol, and also it was demonstrated by the great increase in the urinary norepinephrine output. In addition, bretylium injected intravenously into two dogs depleted of catecholamines by daily intravenous injections of 0.25 mg/kg of reserpine for 5 days failed to produce any rise in blood pressure and heart rate.

In the present studies it was further noticed that the increase in the heart rate in dogs having the buffer reflexes prevented by either TEAC or by denervation persists considerably longer than that which has been reported for dogs having baroceptor reflexes intact. It was found that 3 hours after bretylium injection (10 mg/kg) the heart rate was still much higher than that before injection, and this was reduced readily to control levels within a few minutes by intravenous injection of propranolol. Intravenous injection of propranolol in the dose of 1 mg/kg has been reported by some workers (12) to have a small and transient negative chronotropic effect which is unrelated to its beta receptor-blocking action while others have reported that it has no such effect (13,14). In the present studies, 1 mg/kg of propranolol injected into the chronically reserpinized dogs did not produce changes in blood pressure and heart rate. Therefore, most or all of the reduction of the elevated heart rate after bretylium by propranolol is attributable to its beta adrenergic receptor-blocking action, hence the prolonged elevation in heart rate is due in major part to the action of catecholamines on the sinoatrial node.

In the present studies all dogs except two vagotomized spinal dogs had received large doses of TEAC for the purpose of suppressing buffer reflexes. It is possible that in the later part of each experiment the effect of TEAC might have been diminishing, and so baroceptor reflexes might have been recovering. However, if that were the case, they would tend to cause a decrease in heart rate, rather than to raise it, since the blood pressure remained above the control levels.

TEAC in large doses is said to decelerate the heart rate independently of its ganglion-suppressing action (15); and if so the wearing off of this effect in the later part of each experiment theoretically could result in a rise in a heart rate. However, the heart rate toward the end of the experiments, as at the beginning, could be reduced to the control levels by propranolol. Furthermore, the sustained increase in heart rate after bretylium was observed in vagotomized spinal dogs which had not received TEAC. These results indicate that the gradual decrease in a direct cardiac decelerator action of TEAC played no significant part in the sustained cardiac acceleration which occurred following bretylium injection in ganglioplegic dogs.

The fact that there was no increase in the urinary epinephrine output following bretylium injection is compatible with the interpretation that a catecholamine-releasing action of bretylium in the adrenal medulla plays little or no part in the production of adrenomimetic manifestations following these doses of bretylium. The urinary norepinephrine output following bretylium injection was greatly increased initially. This is in agreement with the reports that bretylium possesses norepinephrine-releasing action. Later on the urinary output of norepinephrine was not significantly higher than that during the preinjection period.

It is reasonable to conclude that the sustained cardiac acceleration following bretylium injection in the ganglioplegic dog is due to the continuous local action of norepinephrine. The prolonged duration of norepinephrine action after bretylium could be related to continuous release of norepinephrine or it could be related to inhibition of uptake of norepinephrine by the nerve endings (3,11), since the latter process is reported to be one of the important mechanisms of reducing levels of circulating catecholamine. Also, bretylium potentiates the effect of injected catecholamines (3,16), possibly by the same mechanism (3). In addition, bretylium has been reported to inhibit monoamine oxidase (17), therefore a decrease in the rate of inactivation of circulating catecholamines might be a factor in causing the prolonged increase in the heart rate.

Summary. Intravenous injection of 10 mg/kg of bretylium produced a sustained elevation of the heart rate in ganglioplegic dogs and in vagotomized spinal dogs and did not have this effect in reserpinized ganglioplegic dogs. At any time after bretylium injection the elevated heart rate could be reduced to the control level by injection of the beta adrenergic receptor-blocking agent, propranolol. The urinary norepinephrine output increased strikingly immediately after bretylium injection and then decreased to control levels, whereas the epinephrine output in the urine was not increased. On the basis of these results the tachycardia throughout the experiments could be attributed largely or entirely to the action of norepinephrine despite the inactivation of the cardioaccelerator pathway.

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Effect of Sotalol (MJ 1999) and Propranolol on Insulin-Induced Hypoglycemia in the Rat (32897)

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Propranolol, an adrenergic β-receptor antagonist (1) currently undergoing clinical trials, has been reported to induce hypoglycemic attacks in normal and diabetic patients (2,3). Abramson *et al.* (4) demonstrated a marked reduction of plasma free fatty acid