Mechanisms of Inhibition of Heart Rate by Phenylephrine


The rationale for using the vasoconstrictor agent phenylephrine to revert paroxysmal auricular tachycardia was that it would be expected to elicit cardioinhibitory reflexes from the rise in pressure in the carotid sinuses and aortic arch.1-3 However, Keys and Violante4 suggested the possibility that phenylephrine "produces a primary bradycardia by inhibition of the sinoauricular node and this is relatively independent of blood pressure reflexes over the vagus nerve." They interpreted results of a later study5 as indicating that phenylephrine "stimulates effectors of both sympathetic and parasympathetic nervous systems—the action of the drug is partly adrenergic and partly cholinergic." A dual basis for the cardioinhibitory action of phenylephrine, as postulated by Keys and Violante, has been referred to in more recent articles as though it is an established fact.6,7 Since the hypothesis of a dual action of phenylephrine seems logical in view of the prominent cardioinhibitory action of the compound, the studies reported here were designed to determine if phenylephrine has an effect on heart rate in some way other than the action elicited reflexly from pressoreceptors.

Methods

All of the studies were performed on dogs weighing between 8 and 12 Kg. They were given morphine sulfate (1.5 mg./Kg.) subcutaneously and within 30 to 45 minutes chloralose (85 to 90 mg./Kg.) was injected intravenously. The concentration of the chloralose solution was 0.9 per cent NaCl solution.

The abdominal aorta was exposed and the branches were tied off along a short segment. Two cannulas were passed in this segment, one toward the heart and the other toward the periphery. Rubber tubing from the 2 cannulas led to a Y tube which was connected by a T tube to a recording mercury manometer, and to the "buffer system." The buffer system consisted of a pressure bottle, containing 0.6 per cent dextran solution, and the air chamber over the solution was connected with a reservoir containing approximately 40 L. of air. Another mercury manometer connected with the air reservoir indicated the pressure. The buffer could thus be set at any specific pressure by introducing air. Movement of 500 ml. of fluid into the buffer system produced a rise in pressure of less than 2 mm. of mercury.

After injecting heparin intravenously, the carotid artery was cannulated with a T-shaped cannula and attached to a mercury manometer. Thus blood flow through the carotid artery was maintained. Initially, the air reservoir of the buffer system was filled to produce a pressure similar to the pressure in the carotid artery of the animal, then the tube connecting the aortic cannula with the system was opened. Blood pressure was recorded simultaneously from the pressure regulator and carotid artery in order to determine if the aortic cannulas were patent and permitting rapid equilibration of arterial blood pressure with the pressure in the regulator. The 2 pressures were recorded simultaneously on a kymographic drum.

In 3 of the experiments the carotid sinuses (and bodies) were inactivated as follows. The common carotid artery was ligated approximately 2 cm. below the bifurcation, and the external and internal carotid arteries were ligated separately approximately 1 cm. above the bifurcation. Then an incision was made into one of the vessels to demonstrate that the blood supply to the sinus had been excluded. The aortic pressoreceptors and chemoreceptors were denervated by sectioning both vagosympathetic trunks high in the cervical region. Vagotomy also results in denervation of other receptors in the atria and left ventricle which might be activated by a rise in pressure following injection of vasoconstrictor agents. When the sino-aortic zones are excluded or denervated by this method intravenous injections of sodium cyanide produce no respiratory stimulation.8 Respiration was recorded by means of a pneumograph and tambour, and heart rate was determined from electrocardiograms (lead II). The number of cardiac cycles was counted for 10-second periods and expressed as rate per minute. In some experi-
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Measurements, simultaneous records of mean blood pressure, heart rate and respiration were obtained by means of a multichannel Sanborn recorder.

Phenylephrine was diluted to 1:5000 in 0.9 per cent NaCl solution and was administered intravenously at constant rates by means of an injection machine. Dibenzyline, a solution of phenoxybenzamine (Smith, Kline and French), was freshly prepared in 0.9 per cent NaCl solution so that 1 ml. contained 1 mg. of the drug. It was injected intravenously during a period of 3 to 5 minutes in doses of 1.0 to 1.5 mg./Kg.

Results

Effects of repeating identical doses of phenylephrine injected rapidly intravenously were determined in 3 dogs under morphine and chloralose and 1 dog which was given morphine alone. In each instance when an injection of phenylephrine was given 15 minutes after the first, a cardioinhibitory response similar in degree and duration to that produced by the first dose was obtained. The maximum slowing occurred between the second and third 10-second interval following the beginning of the injection and the heart rate returned to the initial level in approximately 10 minutes. This demonstrates that tachyphylaxis does not occur when moderate doses of phenylephrine are injected at intervals of not less than 15 minutes.

Effect of Chloralose on Cardioinhibitory Response to Phenylephrine

The effects of rapid intravenous injection of 0.1 mg. of phenylephrine were determined in dogs which had received morphine only and again after intravenous injection of chloralose solution (85 mg./Kg. in 0.9 per cent NaCl solution) or after intravenous injection of equal amounts of 0.9 per cent NaCl without chloralose. The means of rates for the consecutive 10-second intervals are graphed in figure 1. The rate at zero is the control, i.e., that for the 10-second period just preceding the injection of phenylephrine. In all cases, a precipitous decrease in heart rate occurs during the second 10-second period after the injection.

There was an increase in heart rate in 6 of 8 experiments after injection of chloralose solution. However, a greater increase in heart rate was obtained after injecting 0.9 per cent NaCl solution than after injection of chloralose in the same volume of saline solution. Hence, the immediate increase in heart rate following the injection is attributable to the 0.9 per cent NaCl solution rather than to the chloralose.

In 7 of 8 dogs, the extent and duration of the cardioinhibitory response was greater in those under chloralose than in those given saline solution. These results indicate that baroreceptor reflexes are at least as sensitive in dogs under chloralose as in the unanesthetized animal, and it appears that they may be slightly more sensitive.

Change in Effect of Phenylephrine on Heart Rate Produced by Buffering the Arterial Blood Pressure

Thirteen pairs of tests were made on 7 dogs treated with morphine and chloralose. Effects of identical doses of phenylephrine were determined before and during the buffering of blood pressure. The results are shown in figure 2. For each pair of tests, the per cent change in heart rate and per cent change in blood pressure are graphed and the 2 points are connected by a straight line. The upper end of the line in each case is the result obtained when the blood pressure was not buffered. It is seen that a considerable reduction in the pressor response was achieved in all cases by the use of the buffering device, but the blood pressure rise was prevented com-
Effects of Phenylephrine on Heart Rate After Administration of Phenoxybenzamine and During the Buffering of Blood Pressure

Four morphinized dogs were anesthetized with chloralose and the cardioinhibitory response to phenylephrine was compared before and after the intravenous administration of phenoxybenzamine (1.5 mg./Kg.). Before phenoxybenzamine, the average of the blood pressure increases was 20 per cent and the average of the decreases in heart rate was 45 per cent. After this blocking agent, these figures were 4.5 per cent and 21.5 per cent, respectively.

Effects of combining the administration of phenoxybenzamine and buffering of the blood pressure were studied in 5 dogs which had received morphine and chloralose. Phenoxybenzamine (1.5 mg./Kg.) was injected intravenously and the blood pressure was buffered by using the compensator. The increase in mean arterial blood pressure in response to phenylephrine injections did not exceed 3 mm. Hg. In 5 of 7 tests, the change in heart rate was less than ± 2 per cent. In the other 2 animals, the heart rate increased 8 and 12 beats/min.

The results show that no cardioinhibitory effect was produced by phenylephrine when the rise in blood pressure was prevented entirely by use of the buffering device in combination with administration of phenoxybenzamine. In these experiments, the pulse pressure also was not altered.

To test whether phenoxybenzamine might have interfered with the cardioinhibitory response in these animals in some way other than by preventing a rise in blood pressure, Pitressin (3 to 5 units) was administered intravenously. This compound produced a moderate rise in blood pressure and marked cardiac slowing. In 4 dogs the changes in blood pressure and heart rate (in beats/min.) respectively were as follows: +1, −13; +22, −44; +26, −72; +36, −95. These results demonstrate that the cardioinhibitory response through vagal activation still can occur in dogs under phenoxybenzamine.

Discussion

In the present studies, the cardioinhibitory response to phenylephrine was found to be slightly greater in dogs under chloralose than in the unanesthetized controls. That the baroreceptor reflexes retain their sensitivity in dogs under chloralose is to be contrasted with the action of sodium pentobarbital which largely prevents the vagal component of the cardioinhibitory response to vasoconstrictor agents. There is, however, a species difference in the effect of chloralose on the baroreceptors. In cats, chloralose diminishes the sensitivity of the vasmotor center and baroreceptors of the carotid sinus to changes of intrasinusal pressure. In dogs and rabbits, chloralose does not cause any modification of blood pres-
sure response to electrical stimulation of the carotid sinus nerve and aortic nerve. The cardioinhibitory response to intravenously injected phenylephrine is so striking that the suggestion that it exerts this action in some manner other than by means of reflexes from sinoaortic pressoreceptors has been offered. However, in these experiments on dogs in which the increase in blood pressure produced by phenylephrine was counteracted by use of a mechanical buffering device, the cardioinhibitory response was prevented in proportion to the extent that increase in blood pressure was buffered and was prevented in proportion to the degree of loss of pressor response produced by injection of phenoxybenzamine. Phenylephrine had no cardioinhibitory action in any instance when the increase in mean pressure and pulse pressure were prevented completely by the use of the buffering device in combination with moderate doses of phenoxybenzamine. The cardiac slowing which has been observed in vagotomized or atropinized dogs following injection of phenylephrine could have been the result of reflex inhibition of cardioaccelerator tonus from sinoaortic pressoreceptors. Horvath and Knapp suggested that phenylephrine directly alters the activity of the pacemaker since the greatest degree of change in heart rate occurred before the maximum increase in systemic blood pressure. However, if the cardiac inhibition is related solely to reflex effects from pressoreceptors, the greatest inhibition would be expected to occur during the period when the blood pressure is changing rapidly rather than when it reaches a peak.

In some experiments in which phenylephrine was injected and the increase in mean arterial blood pressure was in large part prevented by the compensator, there still was a considerable increase in pulse pressure. The increased pulsations in the sinoaortic zones could be responsible for the slight degree of cardiac slowing occurring in these dogs.

A mild decrease in heart rate sometimes was observed following injection of phenylephrine in sinoaortic denervated dogs not having the blood pressure buffered. To explain this, it could be postulated that reflex inhibition of heart rate is elicited from pressoreceptors other than those which have been denervated. On the other hand, it is possible that pressoreceptors are not concerned and that the increase in blood pressure causes an increase in blood flow through medullary (or higher) brain centers and that consequent alterations in PCO₂ or PO₂ in these centers is the change which causes the decrease in cardioaccelerator tonus. The phenomenon of a decrease in accelerator tonus in sinoaortic denervated animals also has been observed following injections of vasopressin and methoxamine.

**Summary**

Studies were performed to determine the effects of phenylephrine in dogs under chloralose as influenced by mechanical buffering of blood pressure, adrenergic blockade produced by injection of phenoxybenzamine, and combination of the mechanical buffering of blood pressure and phenoxybenzamine administration. Chloralose did not interfere with and possibly mildly sensitized the cardioinhibitory response to phenylephrine. Tachyphylaxis did not occur when moderate doses of phenylephrine were injected at intervals of not less than 15 minutes. Either mechanical buffering or administration of phenoxybenzamine partially prevented the pressor response to phenylephrine, and the cardioinhibitory response correspondingly was less. When the increase in blood pressure was prevented entirely by mechanical buffering of blood pressure combined with phenoxybenzamine administration, phenylephrine caused either no change in heart rate or a mild acceleration. It is concluded that the decreases in heart rate which are observed following injection of phenylephrine, in the doses used in this study, are secondary to the adrenergic actions of the compound.

**Summario in Interlingua**

Essova effectuate studii visato a determinar le effectos de phenylephrine in canes chloralosate, in tanto que ille effectos es influentiate per le tamposion mechanic del tension de sanguine, un blocco...
adrenergic producite per le injection de phenoxybenzamina, e le combination de iste duo mesurs. Le chloralosa lion interfereva in le responsa cardioinhibitori a phenylephrina. De facto, il es possibile que illo causava un leve sensibilisation pro ille responsa. Nullo tachyphylaxe occurreva quando moderate doses de phenylephrina esseva injicite a intervallos de non minus que 15 minutas. Le tamponation mechanic e etiam le administration de phenoxybenzamina preveniva in parte le responsa pressori a phenylephrina, e le responsa cardioinhibitori esseva correspondentemente reduce. Quando le augmento del tension de sanguine esseva prevenite completely per tamponation mechanic del tension de sanguine in combination con le administration de phenoxybenzamina (1) causava nulle alteration del frequentia cardic o (2) un leve acceleration de illo. Es concludite que le declino del frequentin cardic observate post le injection de phenylephrina in le doses usate in le presente studio es secundari al effccto adrenergic de ille composito.

References

1. YOUMANS, W. B., HANEY, H. F., AND AUMANN, K. W.: Relation of the groups of the adrenalin molecule to its cardioaccelerator action. Am. J. Physiol. 130: 100, 1940.
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