Effects of Papaverine upon Ectopic Ventricular Tachycardia Produced by Myocardial Infarction

By A. Sidney Harris, Ph.D., Antonio Estandía, M.D., Abd Bistənī, M.D., and Herbert T. Smith, M.D.

Papaverine hydrochloride exhibited some ectopic impulse suppressor effect which was brief in duration and could not be maintained. Additional doses led to toxic reactions including increased ectopic activity. No consistent correlation was found between changes in blood pressure and decreases or increases in ectopic frequency. Vasodilator potency of drugs apparently bears no intimate relation to ectopic impulse suppressor effect.

LIGATION of the anterior descending artery of the dog's heart by a standard technic1 produces ectopic ventricular tachycardia after a delay of four and one-half to eight hours. Untreated, the tachycardia continues two to four days and there may be some ectopic beats on the fifth day. This persistent ectopic ventricular tachycardia that develops with myocardial infarction is difficult to suppress with drugs, and the standardization of the method has provided an exacting test preparation.2,3,4

It has been shown by other investigators that papaverine raises the fibrillation threshold (intimately related to threshold for premature systoles) of the dog's ventricles to brief direct current stimuli5 and reduces the excitability of the dog's auricles to faradic stimuli.6 The excised papillary muscle of the cat exhibited increased excitability to induction shocks when treated with papaverine in concentrations below $4.5 \times 10^{-2}$ mmol., and excitability was reduced by higher concentrations. Automaticity was induced by the higher concentrations, generally within the range that diminished excitability to shocks.7 Papaverine has been reported effective in abolishing auricular and ventricular premature beats in patients for brief periods,8 but evidence of its action in ventricular tachycardia is meager or lacking.

In the following series of experiments the effects of papaverine hydrochloride upon ventricular tachycardia resulting from myocardial infarction in dogs was tested.

PROCEDURES

Under pentobarbital sodium anesthesia and with aseptic surgical precautions the dog's heart is exposed via an incision in the fourth intercostal space on the left side. The anterior descending artery is dissected free for a distance of about 2 mm. at the level of the free edge of the left auricular appendage. A doubled ligature is then passed under the artery and cut, making two ligatures. A partial occlusion is produced by tying one ligature snugly but not tightly around the artery, together with a 20 gauge hypodermic needle. The second ligature is tied tightly around the artery after an interval of 30 minutes. By this two-stage occlusion technic, losses by early ventricular fibrillation following occlusion are avoided. The chest is closed and the animal is given postoperative care.

Electrocardiograms are made prior to operation and at frequent intervals afterward, especially just before and during tests. On the morning of the first postoperative day, 16 to 20 hours after occlusion, a number of control electrocardiograms are made and testing is begun. At this time almost all animals have a rapid ectopic ventricular tachycardia which is persistent and exhibits only minor changes in frequency from hour to hour. The frequency varies in different animals, from about 150 to 250 per minute. The great majority exhibit frequencies between 170 and 250, but occasional frequencies as high as 300 and lower than 150 are recorded.

The administration of papaverine was by the intravenous route in all tests. Each dose was diluted to 10 cc. with Locke's Solution and injected at a uniform rate during a period of two or five minutes.

From the Departments of Physiology, Louisiana State University School of Medicine, New Orleans, La., and Baylor University College of Medicine, Houston, Tex.

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Results

The effects of papaverine were tested in six dogs, three with low frequency ventricular tachycardias (160 per minute and less) and three with high frequency tachycardias (180 to 250). In experiments with certain other drugs, low frequency ectopic activity has been more easily controlled than the higher frequency tachycardias.\(^2\)\(^,\)\(^3\)

Figure 1 is a chart showing ectopic impulse suppressor effect, brief in duration, 15 to 30 minutes at most, following each of four doses of papaverine in one of the animals with a low frequency ventricular tachycardia, 140 to 160 per minute before treatment. The doses were varied from 3.7 mg. per kilogram in the first injection to 8 mg. per kilogram in the largest one. After the last dose, the ectopic rate tended to level off at about 100 to 110 per minute. No additional doses were given because of the severe vomiting produced by the last two.

In the other two animals in the low-frequency tachycardia group there were brief periods of markedly reduced frequency of the tachycardia or brief restoration of sinus rhythm. The effect could not be sustained, however, even with the administration of additional doses. After a total dosage of about 20 mg. per kilogram additional injections usually increased ectopic activity. In one of these animals the administration of papaverine during periods of sinus rhythm produced ventricular tachycardia, and in certain trials in other animals the ectopic rate was temporarily increased immediately after the injection and diminished a few minutes later. This sequence of changes occurred twice in the same animal after earlier injections had produced only diminutions in frequency. The increase in ectopic activity or the induction of it by papaverine is regarded as one of the toxic manifestations of the drug.

Electrocardiograph and blood pressure records were made continuously during certain injections given to a dog in which papaverine produced ventricular tachycardia. The record made during one of the injections (fig. 2) shows that the paroxysm of tachycardia began just before, or simultaneously with, the beginning of the decline of blood pressure. It did not follow the fall in pressure. Therefore, the tachycardia was not secondary to this reduction. It continued unchanged during the period of increased hypotension. The arterial pressure was already depressed in this animal by the cumulative effects of previous doses of papaverine.

The administration of papaverine to animals with high frequency ventricular tachycardias (180 to 250) also exhibited a small degree of ectopic impulse suppressor effect for brief periods after some doses, and an increase of ectopic activity after other doses. Figure 3 is a reproduction of electrocardiograms from an animal with an ectopic frequency of 240 per minute just prior to the first 10 mg. per kilogram dose of papaverine. The ectopic frequencies in four control records made during the last hour before the beginning of the test ranged between 200 and 250. The tracing in record B shows (in measurement from a longer section) an ectopic rate of 160. This was the lowest ectopic rate achieved during the experiment. It followed the third 10 mg. per kilogram dose. The ectopic frequency in record C made 15 minutes after the fourth dose, is 220. Record D, made immediately after completion of the fifth dose, shows the ventricular fibrillation that developed, apparently as a result of increase in ectopic activity during the fifth injection. This was the only death by ven-
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Ventricular fibrillation that resulted from papaverine administration. The other two dogs with high frequency tachycardias died in cardiac arrest after repeated doses of papaverine, 10 mg. per kilogram, had failed to interrupt the tachycardia even for brief periods.

One death by cardiac arrest occurred after doses totaling 50 mg. per kilogram in two an one-half hours and the other after a total dosage of 60 mg. per kilogram in one and one-half hours. The death by ventricular fibrillation occurred after 50 mg. per kilogram total in two hours.

Blood Pressure. The administration of papaverine, 10 mg. per kilogram, produced a decline in blood pressure in all trials. Each dose was diluted with Locke’s solution to 10 cc. and injected slowly during a period of two minutes or five minutes. The reductions in pressure during and following the five-minute injections ranged from 15 to 35 mm. Hg. The reductions produced by the two-minute injections ranged

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Fig. 2. Continuous record during injection of papaverine showing production of paroxysm of ventricular tachycardia. First arrow designates beginning of injection; second arrow points to beginning of the ventricular tachycardia. Duration of injection extends beyond end of figure. Speed of recording 10 mm. per second.

Fig. 3. Effects of papaverine in animal with high frequency tachycardia.

from 25 to 40 mm. The control pressure usually was not fully regained between doses. Therefore, there was an irregular decline throughout the duration of the tests. There was no consistent correlation between changes in blood pressure and changes in ectopic frequency. Following some injections there was diminution in ectopic rate and in blood pressure. Following certain other injections, there was increased ectopic rate during the diminution in blood pressure.

**Discussion**

Papaverine produced some significant reductions in ectopic frequency in animals with low and moderate frequency ventricular tachycardia and relatively smaller reductions in high frequency tachycardia. These reductions were brief in duration.

The severity of toxic reactions, including increases in ectopic frequency, that resulted from repeated and increased doses given in attempts to obtain lasting suppression of ectopic impulses, indicate that papaverine probably would have little or no practical value for the treatment of ventricular tachycardia accompanying myocardial infarction, and that it could be dangerous if administered in large quantities to patients with high frequency ventricular tachycardia.

The observation, made in the animal in which ventricular tachycardia was produced by papaverine, that the tachycardia began before the blood pressure declined is of interest in regard to the mechanism by which papaverine excites the discharge of ectopic impulses. This observation rules out the possibility that the tachycardia was initiated by a reflex action evoked by hypotension. Other conceivable mechanisms are (1) that papaverine directly excites the myocardium (probably in the frontier of the infarct) to discharge impulses or (2) that it excites the sympathetic nervous system, and possibly the adrenal medulla in some manner not depending upon hypotensive reflex mechanisms. Greiner and Garb\(^7\) have shown that papaverine can induce automaticity in excised papillary muscle of the cat's heart; therefore the sympatoadrenal system need not necessarily be involved, though it might contribute to the total effect.

Some experiments have recently been made with dioxylene phosphate (Pavariil phosphate), which is closely related to papaverine chemically and has greater vasodilator potency, relative to acute toxicity.\(^5, 10\) Dioxylene phosphate failed to exhibit a useful degree of ectopic impulse suppressor action as did nitroglycerin also (both unpublished). It is clear that ectopic suppressor action is not to be anticipated on a basis of demonstrated vasodilator action even though the best known ectopic suppressor compounds (quinidine, procaine amide, magnesium) have vasodilator properties.

**Summary**

Some ectopic impulse suppressor effect was observed following intravenous injections of papaverine hydrochloride to dogs with ventricular tachycardia resulting from myocardial infarction. The effect was brief in duration, and could not be maintained by additional doses.

After a total dosage of about 20 mg. per kilogram in one to two hours, additional doses usually *increased* ectopic activity. Ventricular tachycardia was induced in one animal that had sinus rhythm just prior to the injection of papaverine, and ventricular fibrillation followed shortly after an injection in another. Papaverine has both ectopic impulse suppressor effects and ectopic impulse inducing effects. Neither effect appears to be correlated with the direction of change of blood pressure. Possible mechanisms by which ectopic activity may be produced by papaverine are discussed.

From the study of papaverine and other potent vasodilators, namely dioxylene phosphate and nitroglycerin, it is concluded that useful ectopic impulse suppressor action cannot be anticipated on a basis of vasodilator effect.

**Sumario Español**

Clorhidrato de papaverina mostró tener un efecto supresivo para impulsos ectópicos que fué de duración breve y no se pudo mantener. Dosis adicionales produjeron reacciones tóxicas
incluyendo actividad ectopica aumentada. No se pudo encontrar correlación alguna entre los cambios en presión arterial y decrementos o incrementos en frecuencia ectopica. El poder vasodilatador de la droga aparentemente no tiene relación alguna al afecto supresivo para impulsos ectópicos.

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