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Received September 23, 1952. P.S.E.B.M., 1952, v81.

Experimental Study on Ectopic Beats Following Intravenous Injection of Veratrine.* (19993)

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Subepicardial injection of veratrum alkaloids (veratrine Merck) in the dog's ventricle causes an ectopic rhythm originating in the area of injection. The activity of the ectopic center, firing regular stimuli, is not disturbed by other activation waves spreading over the heart; the center is protected from other stimuli ("protective" block). Thus, a parasystole with simple interference appears regularly(1). On the other hand, true extrasystoles, that is, premature beats with constant coupling to the preceding "initiating" beat(2) were never seen in these experiments. The occurrence of "extrasystoles" following parenteral administration of veratrine has frequently been reported. Since, in general, arrhythmias caused by topical administration of different compounds or electrolytes closely resemble those which appear following the intravenous administration of these substances, we decided to investigate the occurrence of extrasystoles with fixed coupling following intravenous injection of veratridine, cevadine, and a mixture of veratrum alkaloids in the dog.

Method. Dogs weighing 20-25 kg were anesthetized with nembutal and the heart was exposed as described in previous papers by the authors. The right vagus was severed in the neck in each experiment. The electrocardiogram was continuously recorded in Lead II from the time an arrhythmia appeared to the final onset of ventricular fibrillation. Registration was only interrupted when a regular sinus rhythm or a regular tachycardia appeared. A 0.025% solution of the alkaloids was used in all experiments. The solubility of the alkaloids was enhanced by the addition of alcohol. One-tenth of 1 cc of the solution was injected intravenously and if no response appeared within 2 to 4 minutes the injection was repeated in increasing doses up to 1 cc until an arrhythmia was observed. Arrhythmias were seen after injection of about 1.3 mg of veratridine or veratrine Merck. Double doses of cevadine had to be administered in order to obtain the same effect. If no change of the existing arrhythmia was seen after 2 to 4 minutes an additional intravenous injection of the veratrine solution was given. Finally, after 30-50 minutes ventricular fibrillation appeared in all 14 experiments.

Results. In no experiment did we observe extrasystoles with fixed coupling. There were only ectopic ventricular tachycardias with changing form of the ventricular complexes.

Fig. 1a shows the irregularly formed and timed ectopic beats, which—in the last third of the tracing—change into ventricular flutter and fibrillation. Sometimes a bigeminy was suspected as in Fig. 1b and c but closer analysis showed that we are dealing here with other disturbances. A regular sinus tachycardia exists throughout Fig. 1b. The first few complexes show an elevated RS-T segment, presumably due to the appearance of block areas in the myocardium. The same

* This investigation was supported (in part) by a research grant from the National Heart Institute, U. S. Public Health Service.

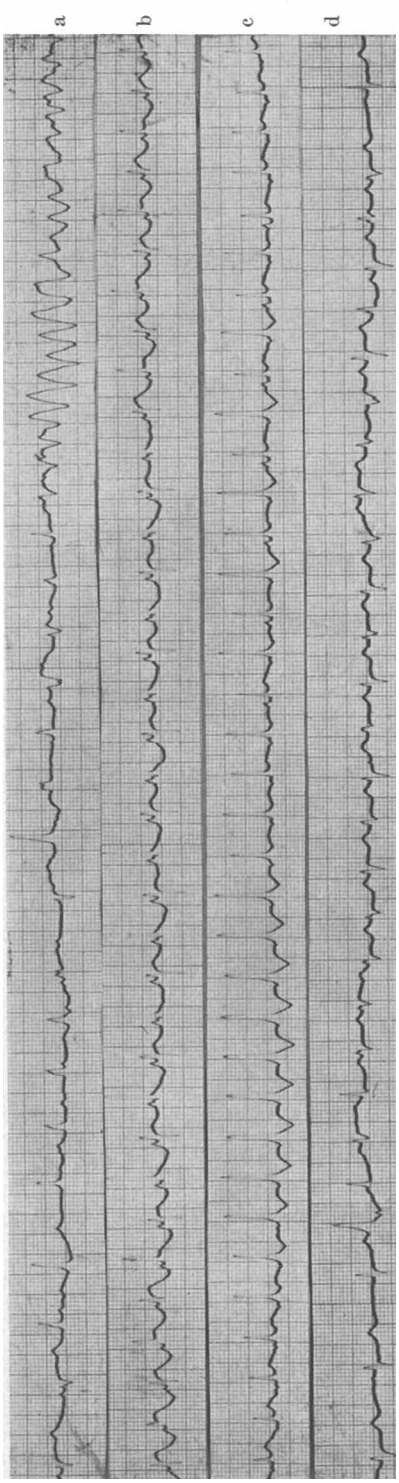

FIG. 1, a–d. The electrocardiographic tracings show different disturbances of ectopic stimulus formation caused by intravenous injection in the dog of veratrine alkaloids. Details are described in the text.

picture is seen at the end of the tracing. In the middle of the tracing 2 forms of the QRS complexes alternate. There is no evidence that every second QRS complex is deformed because of the presence of a ventricular extrasystole appearing late in diastole (combination beat) since the rate of the auricles and ventricles as well as the P-R intervals remains constant. We are dealing with a sinus tachycardia and an electrical alternans due to intraventricular block.

In Fig. 1c a ventricular ectopic rhythm and, later, an auricular bigeminy seem to be present. Closer study of the tracing reveals the presence of an auricular ectopic tachycardia with negative P waves; occasionally, however, positive P waves are seen with every second beat. In some places an abnormal QRS complex seems to follow only the inverted P waves but in other areas the stimuli causing the inverted P waves are conducted normally to the ventricles. We are therefore dealing here with electrical alternation in the auricles and aberrantly conducted ventricular beats but no extrasystoles.

Evidence that the heart in these experiments is under strong veratrine action is afforded by the next tracing. In Fig. 1d a sinus bradycardia appears to be present. Actually a 2:1 block exists. This persisted for about 20 minutes and by an artificial mechanical stimulus applied to the ventricle leading to an extrasystole it could always be transformed into a full rhythm with A-V conduction of every stimulus. Thus a right ventricular extrasystole appears in Fig. 1d after the third sinus beat following a light tap with a probe on the conus of the right ventricle. Immediately the 2:1 block disappears and 23 sinus beats are conducted to the ventricle. The form of the QRS complexes changes due to intraventricular conduction disturbances and a tendency to the appearance of an electrical alternans is present. The P-R intervals also change slightly. The mechanical stimulation was repeatedly applied and each time induced a similar series of conducted beats. The length of these series varied and in some instances numbered 60 beats.

This phenomenon of "deblocking" by an extrasystole has been described only in the veratrinized frog heart(3). It is explained by the fact that the refractory phase of the extra-

systole is short so that the following sinus beat finds the conduction tissue already fully recovered and is conducted to the ventricle. Since this conducted beat appears after a short diastole it also leaves a short refractory phase so that the following beat is also conducted to the ventricle. This goes on for a variable time until a sinus stimulus finds the A-V system again refractory and is blocked. Because of the longer pause which follows, the conducted beats have longer refractory periods and a 2:1 block persists.

Discussion. The tracings described above show that we are dealing with ectopic stimulus formation and intraauricular, intraventricular and A-V conduction disturbances. No extrasystoles with fixed coupling were observed. This finding contradicts the common statement found in the literature that "extrasystoles" appear in veratrine intoxication since only those ectopic beats which are coupled to the preceding beat should be named extrasystoles(2). A study of the literature revealed that all tracings published as demonstrating ventricular extrasystoles actually show irregularly placed ectopic beats(2).

The absence of extrasystoles in these tracings is of interest because an attempt has been made in recent years to explain the appearance of extrasystoles early in diastole by the presence of a supernormal phase of excitability. The supernormal phase of excitability is closely connected with the negative after-potential. Since veratrine is known to increase the negative after-potential much more than any known substance extrasystoles would be expected to appear in these experiments. However, large negative after-potentials with very limited supernormality have been found (4), and it is certain that repetitive firing may exist without a supernormal period and with a depressed excitability(5,6). The objection may be raised that in our experiments the method of anesthesia or the rate of respiration with a resulting alkalosis are responsible for the absence of extrasystoles. Study of the literature revealed, however, that other authors performing their experiments with a different technic and with other veratrine preparations also did not reproduce extrasystoles although they claimed to have done so(2). Injection of 6-8 cc of 0.05 N hydrochloric acid did not change the existing rhythms.

Conclusions. In the experiments reported above the intravenous administration of veratrine alkaloids did not lead to the appearance of extrasystoles with fixed coupling. A review of the literature on this subject did also not reveal this arrhythmia following veratrine. Only irregularly placed ectopic beats, ectopic tachycardias, intra-auricular, intraventricular and A-V conduction disturbances and finally ventricular fibrillation appear. The phenomenon of deblocking of a 2:1 A-V block by an extrasystole was described in the mammalian heart.

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Received October 2, 1952. P.S.E.B.M., 1952, v81.