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Veratramine, an Antagonist to the Cardioaccelerator Action of Epinephrine.

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Hitherto studied adrenolytic substances prevent or abolish the vasomotor effect of epinephrine but are unable to modify its effect upon heart rate. Consistent results, obtained in 10 heart-lung preparations of the dog and in 4 spinal cats, show that veratramine,* [1,2] one of the veratrum alkaloids recently reviewed,[3] prevents or abolishes the cardioaccelerator action of epinephrine in doses which do not abolish its vasopressor effect.

In the heart-lung preparation with a total blood volume of 500 to 900 cc[4] the heart rate can be brought to a steady level of between 200 to 260 beats per minute by the continuous infusion of 0.33 to 0.65 cc of epinephrine 1:100,000 per minute. One milligram of veratramine promptly reduces the rate to or near the normal level without modifying the regular sinus rhythm. (Fig. 1).

The veratramine effect can be overcome, at least partially, by sufficiently high concentrations of epinephrine. Atropine in doses up to 10 mg increases heart rate by 10 to 20%, as in the normal heart-lung preparation, and does not abolish the effect. The veratramine action is long lasting. After one milligram it does not begin to wear off within one hour in the heart-lung preparation. In the pithed cat, however, the effect disappears faster.

After pretreatment with veratramine, ex-

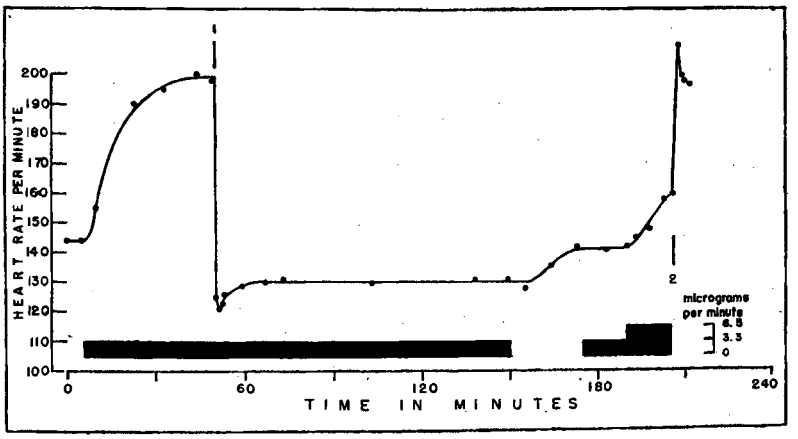

FIG. 1.

Effect of veratramine on cardioacceleration by epinephrine. Heart-lung preparation. Dog, male, 11.6 kg. Total blood volume 800 cc.

Black bar: Continuous infusion of epinephrine tartrate; calibration on right in micrograms of base.

Signal 1: Injection of 1 mg veratramine.

Signal 2: Injection of 500 μg epinephrine (as tartrate) in 5 seconds close to right atrium.

Temperature of blood between 38.6 and 37.6°C.

* Generously supplied by Prof. W. A. Jacobs of the Rockefeller Institute, New York.

1 Saito, K., *Bull. Chem. Soc. Japan*, 1940, **15**, 22.

2 Jacobs, W. A., and Craig, L. C., *J. Biol. Chem.*, 1945, **160**, 555.

3 Krayer, O., and Acheson, G. A., *Physiol. Rev.*, 1946, **26**, 383.

4 For details of method see Krayer, O., and Mendez, R., *J. Pharmacol. and Exp. Therap.*, 1942, **74**, 350.

TABLE I.

Positive Inotropic Without Positive Chronotropic Action of Epinephrine on Heart in Spontaneous Failure Pretreated with Veratramine. Heart-lung preparation. Dog, male, 9.8 kg. Total blood volume 500 cc. Blood temperature between 39 and 38.5°C.

Time	Heart rate per min.	Systemic output* in cc per min.	Systemic output* in cc per stroke	Mean pressure Arterial mm Hg	Mean pressure Pulm. mm water	Mean pressure Right atrial mm water	Remarks
1:27 P.M.	163	420	2.6	80	158	27	
1:29	162	420	2.6	80	158	28	Between 1:38 and 3:45 8,5 mg veratramine adm. in divided doses
3:45	105	220	2.1	68	240	76	3:45 heart rate regular, normal sinus rhythm
3:47	105	205	2.0	67	242	77	3:47' 55-60" 10 μg epinephrine inj. in 5 sec. (as tartrate)
3:48	105	450	4.3	78	185	19	
3:49	95	420	4.4	78	185	21	
3:51	93	390	4.2	77	198	27	
3:54	96	360	3.8	75	206	34	
3:57	98	330	3.4	72	225	44	
3:58 0- 5"							3:58' 0-5" 30 μg epinephrine inj.
10-20"	110			84			
20-30"	127			78	173	10	
30-60"	97			76	185	15	
3:58 total	105	530	5.2†				
3:59	95	440	4.6	76	175	11	
4:01	95	430	4.5	76	180	13	

* Systemic output = total output of left ventricle minus coronary flow.
† Average stroke volume.

perimental heart failure can be relieved by epinephrine without cardioacceleration. (Table I.). In the normal heart-lung preparation 10 and 30 μg (as used in the experiment of Table I) lead to a maximal heart rate increase of at least 20% and 40% respectively; 10 to 15 and 20 to 30 minutes respectively are required for the initial rate to return. It is thus possible to separate the positive chronotropic from the positive inotropic effect of epinephrine. The rate of disappearance of epinephrine appears unchanged, as the positive inotropic action lasts as long as without the presence of veratramine.

Of other veratrum alkaloids studied jervine in a dose of one mg gave an effect similar to 0.1 mg of veratramine, while cevine in a dose of 40 mg was ineffective under the same conditions.