The Influence of Hexamethonium Intracisternally and of Hexamethonium and Trimethaphan Camphorsulfonate Intravenously on the Pressor Responses to Intracisternal Veratrine* (34083)

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Jarisch and Richter (1) found that after repeated doses of veratrine and vagal blockade, veratrine frequently produced a rise in blood pressure and acceleration of the heart. The same authors (2) injected small doses of veratrine into the fourth ventricle of dogs and cats by way of the cisterna magna and noted a marked rise in systemic arterial pressure, increased secretion of adrenalin, and pulmonary edema.

Aravanis *et al.* (3) were able to produce acute pulmonary edema in the dog under intravenous chloralose anesthesia by injecting veratrine in a dose of 40 μg/kg into the fourth ventricle via the cisterna magna. They were able to prevent the occurrence of the edema by excluding the systemic circulation by ligation of the upper thoracic aorta and the inferior vena cava above the diaphragm. Their explanation for the occurrence of the edema was that the intense stimulation of the brain by veratrine resulted in a severe peripheral vasoconstriction and shifting of the blood from systemic circulation into the pulmonary vascular bed.

Sarnoff and Sarnoff (4) and Sarnoff *et al.* (5) found that the intravenous administration of trimethylene thiophanium D-camphor sulfonate as a ganglionic blocking agent counteracted the rise in systemic and pulmonary pressures that had been produced by the intracisternal injection of a thrombin–fibrinogen mixture.

In a preliminary communication (6) we have reported that hexamethonium in doses mainly of 5 mg/kg cisternally prevented the rise in blood pressure from subsequent cisternal injections of veratrine but that 5 to 10 mg/kg hexamethonium intravenously did not. The pressor response was effectively blocked by phentolamine in doses of 2–5 mg/kg indicating a sympathetic-like mechanism of the hypertension. The present study is an extension of the work to include the effects of 2 mg/kg of hexamethonium intracisternally on effects of subsequent cisternal injections of veratrine and the effects of large doses of hexamethonium and trimethaphan camphorsulfonate intravenously on the pressor responses.

Methods. Forty-five mongrel dogs of both sexes weighing from 9–18 kg were studied under pentobarbital anesthesia (30 mg/kg). Arterial pressure was recorded from a femoral artery on a Statham transducer and Sanborn recorder. Positive-pressure artificial respiration was maintained throughout the experiments. Saline in doses of 0.1 cc/kg or veratrine in doses of 0.1 mg/kg in a 1:1000 dilution was injected intracisternally after withdrawing equivalent amounts of spinal fluid. One group of nine animals (A) was injected intracisternally with control doses of saline followed in 10–20 min by intracisternal injection of veratrine. In a second group (B), ten dogs were injected intravenously with 10 mg/kg hexamethonium chloride 10 min prior to intracisternal injection of veratrine. The degree of ganglionic blockade was verified by the intravenous administration of 75–100 μg/kg of nicotine. A third group (C), of 14 dogs was injected intracisternally with 2 mg/kg hexamethonium chloride 10 min

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TABLE I. Blood Pressure Responses to Intracisternal Injections of Veratrine as Modified by Intravenous or Intracisternal Injection of Hexamethonium Chloride.

	Systole	Diastole	Mean
Group 1 (9 dogs)			
Control	168 ± 12	118 ± 8	134 ± 8
Saline	165 ± 13	118 ± 10	134 ± 11
Veratrine	306 ± 40	187 ± 15	227 ± 24
Group 2 (10 dogs)			
Control	176 ± 18	107 ± 53	137 ± 15
10 mg/kg hexamethonium chloride iv	140 ± 22	87 ± 16	105 ± 17
Veratrine	277 ± 71	157 ± 25	197 ± 39
Group 3 (14 dogs)			
Control	174 ± 26	111 ± 17	132 ± 19
2.0 mg/kg hexamethonium chloride ic	148 ± 25	94 ± 18	112 ± 19
Veratrine	162 ± 51	107 ± 48	125 ± 52

prior to the injection of veratrine by the same route. Nicotine in doses of 75–100 μg/kg was given intravenously to test for possible ganglionic blockade.

In a fourth group of 12 dogs prepared as above the sympathetic chain and splanchnic nerves were exposed. The maximum pressor response to splanchnic nerve stimulation and the responses to carotid occlusion and nicotine in doses of 75–100 μg/kg were determined. Trimethaphan camphorsulfonate was given by slow intravenous infusion until the degree of blockade was adequate to prevent pressor responses to all three of the above parameters. The response to cisternal injection of 0.1 mg/kg of veratrine was then determined.

Results. Group A. As seen in Table I and Fig. 1 the intracisternal injection of saline produced little or no pressure changes. Subsequent injection of veratrine by the same route produced a marked increase in both systolic and diastolic pressures along with a slight increase in heart rate. The pressures rose from an average of 141/90 to 288/154 (Fig. 1). Peak pressures were attained in 2–6 min. The pressure remained elevated above controls for up to 20 min after which the pressure fell suddenly and the animal died. In group B, effective ganglionic blockade after intravenous hexamethonium was demonstrated by a lack of pressor responses to 75 μg/kg of nicotine. Subsequent injection of veratrine intracisternally produced, as shown in Table I and Fig. 1, rises of pressure from control levels of 140/93 to 277/157. While the pressure was subsiding, injection of 75 μg/kg of nicotine showed that the ganglia were still blocked to this dose of the drug.

In the third group of animals (C) 2 mg/kg of hexamethonium intracisternally did not modify the pressor response to 75 μg/kg nicotine intravenously. Intracisternal injection of veratrine 10 min subsequent to hexamethonium by the same route produced only slight rises in systolic and diastolic pressures with no change in heart rate (Table I and Fig. 1).

In the fourth group of dogs levels of trimethaphan camphorsulfonate that blocked the pressor response to splanchnic stimulation, carotid occlusion, and nicotine injection depressed but did not block the pressor response to cisternally injected veratrine in seven animals. In these the pressures had fallen to a mean of 57/30 mm Hg and rose to a mean of 168/96. In five dogs additional blocking agent was given that lowered the pressures to a mean 20/10 mm Hg. No pressor response to cisternally injected veratrine was seen in these animals.

Discussion. The failure of hexamethonium given intravenously to effectively block the pressor responses to the intracisternal injection of veratrine (Fig. 1 and Table I) is in keeping with our previous experience (7)

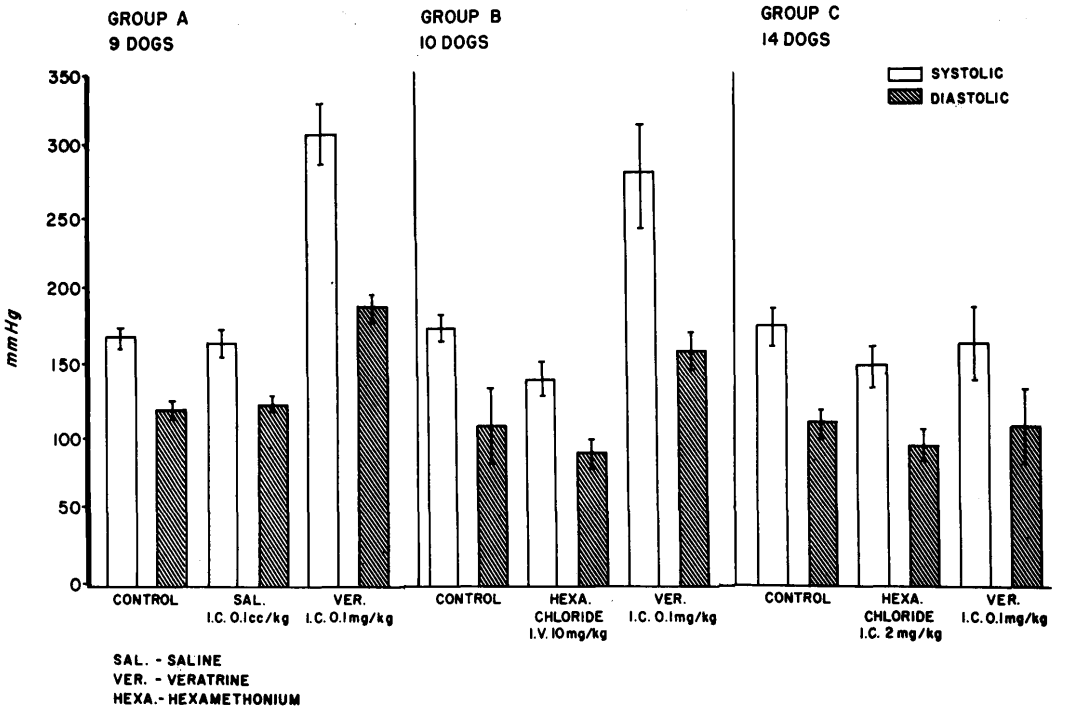

FIG. 1. Blood pressure responses to intracisternal injection of veratrine as modified by intravenous or intracisternal injection of hexamethonium.

that this agent in large doses was inadequate to prevent pulmonary edema in rats and the marked pressor responses and pulmonary edema in dogs which followed the preoptic injection of aconitine. Peripheral sympathetic blocking agents, dibenzyline, and phentolamine did however prevent the rise in pressure and largely prevented edema formation.

Our experiments indicate that doses of trimethaphan camphorsulfonate that effectively block the effects of splanchnic stimulation, carotid occlusion, and nicotine, produces marked degressor effects but only partially blocks the pressor effects of cisternally injected veratrine. Larger doses of this blocking agent that produces severe depression of blood pressure are required to block the pressor response to cisternally injected veratrine. Our experiments would suggest that doses of hexamethonium which prevent the pressor response to 75–100 μg/kg of nicotine either do not effectively block ganglionic transmission of strong centrally induced impulses or that vasopressor materials are being released by other mechanisms. The fact that artificial respiration was maintained throughout the experiments rules out the respiratory influence on circulatory responses. Moe *et al.* (8) showed that artificial respiration does not modify the blood pressure responses to veratrine. There is considerable evidence that certain autonomic pathways are invulnerable to ganglionic blockade. These include the accelerator pathways to the atrio-ventricular node after removal of the sinus area, the pathways involved in asphyxial rise in blood pressure, and motor fibers to the upper small intestine (9). There is also evidence that under certain circumstances ganglionic blocking agents may themselves produce pressor actions or potentiate the effects of other pressor agents (10).

The finding that intracisternal injection of hexamethonium (Table I, Fig. 1) prevents the hypertension from subsequent injection of veratrine by the same route indicates the vulnerability of pressor sites in this area of the brain to a ganglionic blocking agent. The pressor and depressor sites in the brain stem

have been studied by many investigators in anesthetized animals (11–13). Gutman *et al.* (14) studied pressor and depressor sites from the hypothalamus to medulla in unanesthetized rabbits and found a dominance of pressor sites. Many pressor sites, however, became depressor under the influence of anesthesia. Our experiments to date leave unanswered the question of the extent of the surface of the brain stem involved and the depth of penetration of hexamethonium to underlying pressor centers.

Summary. The pressor responses to cisternally injected veratrine in dogs was effectively blocked by previous cisternal injection of hexamethonium in doses of 2 mg/kg but not by intravenous doses of 10 mg/kg. A different ganglionic blocking agent, trimethaphan camphorsulfonate, in intravenous doses just adequate to block the effects of carotid occlusion, splanchnic stimulation, and nicotine injection, and which produced a marked fall in blood pressure, partially blocked the pressor response to veratrine. Additional doses of the blocking agent which produced severe blood pressure depression were required to completely block the veratrine pressor response.

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