Comparison of Hypotensive and Emetic Dosages of Cryptenamine and Other Veratrum Extracts in Humans.* (20651)

FRANK A. FINNERTY, JR. (Introduced by Edward D. Freis.)
From the Department of Medicine, Georgetown University School of Medicine, the Georgetown and George Washington University Obstetrical Divisions, the Gallinger Municipal Hospital, Washington, D. C.

Various alkaloids of the Veratrum group have been shown to exhibit a close relationship between the amount required to lower blood pressure and that required to produce emesis.(1) Recently, however, the alkaloid Cryptenamine, isolated from veratrum viride, was shown in animal investigations to have a ratio of approximately 4:1 in regard to hypotensive and emetic dosages.(2) It was decided, therefore, to determine whether this alkaloid exhibited a similar divergence between the hypotensive and emetic dose in the human.

Materials and methods. Fifty-one hospitalized patients received various extracts of veratrum viride administered intravenously, and 386 patients received the same extracts intramuscularly. In the intravenous group, 21 patients received Cryptenamine and 30 patients received mixtures of the amorphous alkaloids of veratrum viride (15 received Vergitryl, and 15, Veriloid). The diagnoses included toxemia of pregnancy (29), hypertensive encephalopathy (14), and acute glomerulonephritis (8). When given intravenously, 1 mg of each Veratrum extract was diluted with 19 cc of 5% dextrose in water, and the solution was given at a rate of 1 cc or .05 mg per minute until the first 20 mm reduction in systolic or 10 mm reduction in diastolic pressure occurred. Additional Veratrum was not given for a 2 minute period in order to avoid a precipitous fall in blood pressure. If, after waiting 2 minutes, no further reduction in arterial pressure occurred, administration was continued at a rate of .05 mg per minute, stopping at the first subsequent sign of hypotension. In eclamptic patients, administration was continued until the blood pressure fell below 140/90 mm Hg, and in other cases until the pressure fell below 160/110 mm Hg. Dosages were resumed whenever the blood pressure rose above these levels, and treatment was continued for from 1 to 5 days using this intermittent intravenous technic. Of the 386 patients who received these Veratrum extracts intramuscularly, 97 were given Cryptenamine, 233 received Vergitryl, and 56 received Veriloid. All the patients were pregnant; 283 were diagnosed as toxemia of pregnancy, 103 as hypertensive vascular disease. The dosage used was 0.5 mg repeated every hour if necessary to keep the blood pressure under 140/90 mm Hg. The clinical results are given in detail elsewhere (3,4).

Results. The incidence of vomiting following intravenous injection of the various extracts is given in Table I. Following the initial injection of Cryptenamine, 4 of the 21 patients (21%) vomited. Emesis occurred after the initial injection in all of the patients treated with Vergitryl and in all of those treated with Veriloid. Nine patients (43%) of the group given Cryptenamine developed vomiting when repeated injections of the drug were given. Fourteen patients (93%) of the Vergitryl group and 13 patients (87%) of the Veriloid group manifested vomiting on repeated intravenous administration. The average dose of the 3 drugs was essentially the same.

In contrast to these results observed after intravenous injection, the incidence of vomiting observed following intramuscular administration was essentially the same with each of the 3 extracts of veratrum viride (Table II).

Discussion and conclusions. Clinical experience with purified alkaloids of veratrum prior to the synthesis of Cryptenamine showed that there was a relatively low incidence of vomiting following intramuscular administra-

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TABLE I. Incidence of Vomiting Following Veratrum Extracts Administered Intravenously.

Drug	No. of patients: Toxemias of pregnancy	Hypertensive encephalopathy	Nephritis	Avg effective dose, mg	No. patients showing vomiting on 1st inj.	%	No. patients vomiting on repeated inj.	%
Cryptenamine	15	4	2	.3	4	21	9	43
Vergitryl	8	4	3	.3	15	100	14	93
Veriloid	6	6	3	.4	15	100	13	87

TABLE II. Incidence of Vomiting Following Veratrum Extracts Administered Intramuscularly.

Drug	No. patients	Avg dose, mg	No. of patients vomiting	%
Cryptenamine	97	.5	8	7
Vergitryl	233	.5	27	11
Veriloid	56	.5	3	7.5

tion. When a veratrum preparation was given intravenously, however, though a smaller total dose was required to lower blood pressure than when it was given intramuscularly, the incidence of vomiting was greatly increased. It was observed further that vomiting occurred most frequently following the initial intravenous injection.

When given intramuscularly, Cryptenamine resembled the other veratrum alkaloids both in hypotensive effect and incidence of vomiting. When given intravenously, however, it differed from the other alkaloids since moderately rapid administration caused significantly less vomiting particularly following the initial injection. Our data showed that none of the veratrum alkaloids were particularly emetic when their absorption was slowed, but that the receptors initiating emesis were especially sensitive to the sudden higher concentration presented to it when the drugs were given intravenously. It was only in this respect that Cryptenamine differed from the other alkaloids studied. It is concluded, therefore, that the divergence between the hypotensive and emetic dose of Cryptenamine reported in animals also exists in man, and is most apparent after intravenous administration wherein vomiting is common with the other veratrum alkaloids.

1. Swiss, E. D., and Maison, G. L., *J. Pharmacol. and Exp. Therap.*, 1952, v105, 87.

2. Cavallite, C. J., and O'Dell, T. B., personal communication to the author.

3. Finnerty, F. A., Jr., *New Eng. J. Med.*, 1952, v246, 646.

4. Finnerty, F. A., Jr., Fuchs, G. J., Jr., *Am. J. Obst. and Gynec.*, 1953, in press.

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Effect of Immobilization on Oxygen Uptake of Skeletal Muscle.*† (20652)

FRED L. HUMOLLER, DOROTHY HATCH, FREDERICK WARE, JR., AND A. R. MCINTYRE.

From the Department of Physiology and Pharmacology, University of Nebraska College of Medicine, Omaha, Neb.

It has been shown(1) that following denervation of the gastrocnemius muscle the cytochrome oxidase activity of this muscle decreased progressively with time. Since these findings did not agree with the results reported by other laboratories(2-4), it seemed desirable to determine the effect of immobilization under conditions which would rule out any contributory effect of fibrillation on the oxygen uptake of the muscle studied.

It also appeared desirable to approach the problem from the opposite angle, *i.e.*, to determine the oxygen uptake of a denervated muscle subjected to constant passive move-

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