Biological Properties of Cryptenamine, A New *Veratrum viride* Alkaloid Preparation. (20894)

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Of the many major and minor alkaloids reported from *Veratrum viride* and related species, those for which pharmacological data are available showing hypotensive properties also show marked side reactions of nausea and vomiting at effective hypotensive doses. A new group of alkaloids has been reported(1) for which an appreciable ratio exists between hypotensive and emetic doses as demonstrated in dogs. The test methods used and results obtained are herein reported.

By means of the non-aqueous extraction methods developed in these laboratories, new alkaloids have been isolated from *Veratrum viride* which consist of ester alkaloids of bases previously reported as being present only as alkamines. This preparation has been given the generic name cryptenamine (trade name Unitensen), and the chemistry will be reported elsewhere(2).

Methods. I. Determination of effective hypotensive dose (C.S.R. unitage). The procedure used in determining the effective hypotensive dose has been published(3). The only variation from the published procedure is in the dose increment used. Cryptenamine is assayed in dogs by the intravenous administration of dose increments of the order of 0.002 mg/kg and the end-point determined as described previously(3). The solution for assay is prepared so that each cc contains 0.1 mg of alkaloid. This is then administered in 0.02 cc/kg (0.002 mg/kg) increments. Potency is expressed as C.S.R. Units/mg of alkaloid. II. Determination of emetic dose. Animals: unanesthetized mongrel dogs (5 per assay). Route of administration: Intravenous. Dosage: dose increments 3 times those used for the determination of potency. The time interval between injections is 10 minutes.

During the experimental work, in determining the best procedure for measuring the emetic dose, variations were made in both the dose increment and the time between injections. The dose per injection was varied from the same dose as used for the determination of potency (C.S.R. unitage) to 4 times this dose. The time interval between injections was varied from 5 to 10 minutes. The results were essentially the same. The larger dose was chosen since the amount of drug necessary to produce emesis is so much greater than that producing the C.S.R. end-point. A 10-minute time interval was chosen to allow maximum time for emesis to occur between injections and still not lose the effect of previous doses.

Results. These alkaloids are consistent and predictable in their biological behavior. The variations observed from one animal to another using the same alkaloid sample are well within the limits of biological error and there is very little variation among different samples of the alkaloid preparations.

In dogs, the hypotensive action of these alkaloids usually occurs as a primary and secondary blood pressure fall. The duration of the primary fall is 10 to 20 minutes during which time a partial recovery of the blood pressure has taken place. The duration of the secondary fall is a matter of hours.

As is well known, the most frequent side reactions of the *veratrum* alkaloids are nausea and vomiting. These new alkaloids are unique in that the amount necessary to produce emesis in the dog by the intravenous route is approximately 4 times the effective hypotensive dose in the dog. These are the first alkaloids or alkaloid preparations for which a ratio this large has been described. It has also been noted that the emesis produced by these alkaloids is less intense and of shorter duration than that produced by other alkaloids or alkaloid preparations.

In addition to the increased ratio between the emetic and effective doses of these alkaloids, they appear to be less toxic relative to their effective doses. The comparisons of

TABLE I. Comparison in Animals of Cryptenamine Alkaloids with Protoveratrine and Veriloid[R].

Preparation	Effective dose mg/kg*	Stand. error	Emetic dose mg/kg*	Stand. error	Emetic ratio†	I.V. toxicity mice (mg/kg) LD_{50}‡	LD_{100}
Secondary fraction—cryptenamine	.0081 (50)	.00014	.034 (25)	.0014	4.2:1	.64	1.06
Tertiary fraction—cryptenamine	.0052 (30)	.00019	.018 (15)	.00082	3.5:1	.6	1.0
Protoveratrine	.005 (5)	.00022	.0052(5)	.00033	1 :1	.047	.052
Veriloid[R]	.015 (10)	.0014	.018 (5)	.0023	1.2:1	.43	.6

* Figure in parentheses indicates No. of animals used.

† Ratio $= \frac{\text{Emetic dose}}{\text{Effective dose}}$.

‡ Calculated using method of Behrens(4).

these new alkaloids with protoveratrine and Veriloid[R] as regards emetic ratio and intravenous toxicity in mice are shown in Table I.

Discussion and conclusions. It has been a generally held opinion that the hypotensive and emetic properties of *Veratrum* alkaloids were inseparable properties dosewise. For the first time there has been demonstrated an appreciable difference between the emetic and effective hypotensive doses of *Veratrum* species alkaloid preparations. The existence of this emetic/effective dose ratio is not only of interest therapeutically, but suggests that the mechanisms of emetic and hypotensive actions of *Veratrum* alkaloids are not necessarily interrelated.

This difference between the emetic and effective dose also has been demonstrated in humans. Finnerty(5) recently reported that a difference does exist, and is more apparent after intravenous administration of cryptenamine.

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Effect of Choline Deficiency and Hepatic Cirrhosis on Absorption of Fat in the Rat. (20895)

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The following experiment was undertaken to determine whether alimentary absorption of fat is decreased in rats having prolonged and severe choline deficiency and marked fatty vacuolization of the liver, or in rats having associated severe cirrhosis of the liver. Tidwell(1) found decreased fat absorption in rats which were mildly choline deficient, and increased absorption of fat in similar rats after they received choline supplements. Shoshkes, *et. al.*(2), did not demonstrate any difference in the absorption of corn oil by choline deficient rats, as compared with normal animals.

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