Clinical Studies on Veratrum Alkaloids

I. The Action of Protoveratrine and Veratridine in Hypertension

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The action of two pure veratrum alkaloids, veratridine and protoveratrine, in human hypertension is described for the first time. The vasodepressor reflex pathway involved in the response to these ester alkaloids is reviewed. Protoveratrine is found to produce a striking fall in blood pressure in both essential and renal hypertension after intravenous administration.

The use of veratrum alkaloids in clinical medicine began many years ago for a variety of indications because of their ability to decrease blood pressure and heart rate, to induce sweating and reduce the body temperature, and to prevent certain types of convulsions, especially those of eclampsia. MacNider quotes the old clinical observation concerning the use of veratrum alkaloids in eclampsia: that if the “pulse was kept at or below sixty-five beats per minute, the patient could not have convulsions.”

The clinical use of veratrum alkaloids has generally fallen into disrepute mainly for two reasons. The alkaloid content and composition of the plant extracts, called veratrum, vary greatly and reliable methods of standardization of the active principles are not available. Veratrum causes severe toxic reactions such as nausea, vomiting, and unpredictable and sometimes profound fall in blood pressure.

Despite these drawbacks certain obstetric clinics have continued to use veratrum viride as an adjunct in the treatment of eclampsia. More recently, there has been a revival of the use of veratrum viride in the treatment of hypertension, stimulated by experimental, pharmacologic work, which has led to a clarification of the mechanism of action of some of the veratrum alkaloids.

Nomenclature. In this and subsequent publications the terms “veratrum alkaloids,” “veratrum,” and “veratrine” will be used in conformity with the suggestions made by Krayer and Acheson. The term “veratrum alkaloids” refers to all alkaloids found in any of the Veratrum species.* The term “veratrum,” which for some time was an official name, refers to the galenical preparations of certain species of Veratrum. The two most commonly used and best known preparations of veratrum are “veratrum viride” from Veratrum viride, Aiton, and “veratrum album” from Veratrum album, Linn. The term “veratrine” refers to the mixture of alkaloids obtained from the seeds of Veratrum sabadilla, Retz., more commonly known as Schoenocaulon officinale, Gray.

Reflex Vasodepressor and Cardiodecelerator Action. The reflex pathways commonly considered to regulate arterial pressure are those arising in the pressoreceptor areas of the carotid sinus and of the aortic arch. Their importance as moderators of blood pressure is well known since the work of Hering and of Heymans and Bouckaert.

A similar vasodepressor reflex pathway which arises in the heart and has afferent fibers in the vagus nerve has not yet received much attention in the English and American literature. The evidence for the existence of this vasodepressor reflex is largely based on studies of the effect of veratrum alkaloids.

Von Bezold and Hirt described a vasode-
pressor and cardiodecelerator action of veratrine in 1867 in laboratory experiments and attributed it to a reflex originating in the heart. This was generally forgotten until Jarisch and Richter\textsuperscript{12} restudied it in 1939. Like von Bezold and Hirt they concluded from their experiments that the reflex decrease in heart rate and in blood pressure caused by small doses of veratrine originated predominantly in the ventricular myocardium and that the afferent impulses were carried by nerve fibers running in the vagus nerves. Jarisch and Richter proposed the name “Bezold effect” for this phenomenon.

Further evidence for the existence of such a reflex pathway came from the work of Amann and Schaefer\textsuperscript{9} who demonstrated afferent fibers in the cardiac branches of the vagus which carried bursts of electrical activity in phase with the heart beat. These discontinuous discharges could be changed to a continuous discharge by the action of veratrine. Jarisch and Zottermann\textsuperscript{10} have recently corroborated this observation and have further elucidated the nature of the nerve fibers.

Krayer and his collaborators\textsuperscript{11, 12, 13} have confirmed and extended the pharmacologic work, using not only veratrine and veratrum viride but also pure veratrum alkaloids. It was shown in experimental animals that not all veratrum alkaloids but only some of the ester alkaloids like protoveratrine (from \textit{Veratrum album}, Linn) or veratridine (one of the constituent alkaloids of veratrine) were capable of eliciting the reflex decrease in blood pressure and in heart rate, and that it was essential to use small doses to obtain the effect in its purest form. While the afferent impulses caused by veratridine\textsuperscript{11} and protoveratrine\textsuperscript{12} originated predominantly in the heart and lungs, a participation of the carotid sinus area also was suggested by some of the experiments. This was recently established by Aviado and Pontius.\textsuperscript{14}

By localized injections of protoveratrine and veratridine into sections of the coronary vessels, Dawes\textsuperscript{13} was able to show that the most important receptor area for this reflex was in the region of distribution of the left coronary artery of the dog and cat and, more precisely, in the area of the left circumflex branch, that is, in the left ventricle.

The efferent pathways of the reflex are are known only in part. The cardiodecelerator impulses are carried by fibers running in the vagus and cardiodeceleration can be abolished by atropine.

The increased blood flow in various vascular areas which accompanies the blood pressure fall is due to nervous influences and not to a direct action of the alkaloids upon the vasomotor effector in the vessel wall. The mechanism by which the vasodilatation is brought about is unknown; to what extent decrease in vasomotor discharge, or vasodilatation by some other mechanisms, is involved has not been elucidated.

The receptors for this reflex pathway have not yet been anatomically demonstrated, and no reliable information is at hand as to its physiologic and pathologic role. The existence of a receptor mechanism in the left ventricle, the stimulation of which leads to a fall in blood pressure, suggests the possibility of its participation in such clinical phenomena as the profound fall in blood pressure attending severe episodes of coronary artery disease with and without infarction, or the rare return to normal or near normal pressure in the hypertension of a patient who has had a myocardial infarction.

\textit{Necessity for the Use of Pure Substances.} The pharmacologic studies with pure veratrum alkaloids have revealed that several distinct properties of the alkaloid mixtures, veratrine, veratum viride, or veratrum album, are vested in different alkaloids or alkaloid groups; hence many of the pharmacologic and clinical observations with such alkaloid mixtures were obviously due to the composite action of various substances.

We have undertaken the clinical study of the ester alkaloids, protoveratrine and veratridine, because we believe that “only the study of the pure veratrum alkaloids will permit a correct evaluation of the practical usefulness of the pure alkaloids as well as of their mixtures, and thus make possible the development of a rational basis for their clinical use.”\textsuperscript{14} Furthermore, the disagreeable side effects of veratrum
viride or veratrum album probably are vested in certain alkaloids to a higher degree than in others. This is suggested, for example, by the difference in the respiratory action of protoveratrine and veratridine in laboratory animals. The search for compounds with desirable therapeutic action and devoid of side effects can only be successful if pure substances are investigated individually.

The following is a report of studies in human hypertension in which protoveratrine has been used for the first time. A number of observations were made with veratridine, which was employed earlier in a few clinical trials.*

**Substances and Methods**

As has been shown by Craig and Jacobs,16 Prelog and Szpilfogel,17 and Roehmeyer,18 the veratrum alkaloids are modified sterols and their alkamines have a chemical relation to the genins of the cardiac glycosides.

Protoveratrine is a crystalline substance, C_{28}H_{40}O_{3}N. It is an ester alkaloid of the alkamine protoveratrine and the three acids, acetic acid, methylacetic acid, and methylglycolic acid. It is one of the main alkaloids of Veratrum album and has not yet been isolated from Veratrum viride. It is the most poisonous of the veratrum alkaloids so far studied and on intravenous injection in mice has an LD_{50} of 0.06 micromols (= 0.048 mg.) per kilogram.13

Veratridine is an amorphous alkaloid, C_{28}H_{40}O_{3}N. It is an ester of the alkamine cevine and one molecule of veratic acid. It is one of the alkaloids of veratrine and has not been found in either Veratrum viride or Veratrum album. Its toxicity is less than that of protoveratrine. On intravenous injection in mice it has an LD_{50} of 0.63 micromols (= 0.42 mg.) per kilogram.13

The sample of protoveratrine used in this study was prepared from Veratrum album, Linn., by W. A. Jacobs of the Rockefeller Institute for Medical Research. The sample of veratridine was isolated from veratrine, Merek, by R. P. Linstead and D. Todd of the Department of Chemistry, Harvard University. The same samples of protoveratrine and veratridine were used in their pharmacologic studies by Krayer and his collaborators. For clinical use the alkaloids were brought into solution with N/10 hydrochloric acid and adjusted to a concentration of 1:1000 (veratridine) or 1:10,000 (protoveratrine) with distilled water. The solutions were kept at pH 6 and were sterilized by filtration through a fritted glass. Maintained at 6°C. they were stable for three months.

Protoveratrine was administered by intravenous injection. One hundred sixty-eight experiments were made in 26 patients, most of them outpatients who came in for the experiments. The highest single intravenous dose given at one time was 0.20 milligram.

Veratridine was administered to 14 patients, seventeen times intravenously and seven times intramuscularly.

All blood pressure measurements were made by the same observer (E.M.) with the mercury sphygmonanometer keeping the patient in a recumbent position. Continuous observation of the electrocardiogram was made possible by the use of a cardioscope.

**Results**

**Protoveratrine**

**Vasodepressor Action.** Protoveratrine when administered intravenously in suitable dosage produces a fall in both systolic and diastolic pressure which is reproducible on repeated use of the same dose. Figure 1 illustrates the response of systolic blood pressure, diastolic blood pressure, and heart rate in a 50 year old woman with essential hypertension for at least five years, possibly fifteen years, who received 0.107 mg. intravenously on each of five occasions, two of them on the same day. The fall in blood pressure produced is essentially the same each time, and it is usually maximal in the first ten to fifteen minutes. Similar results were obtained in other patients with renal hypertension as well as essential hypertension. A 42 year old woman who had chronic glomerulonephritis for twelve years, during the last six of which she gradually developed hypertension, received the same dose (0.107 mg.) on each of four successive days and the response was essentially the same each time.

The amount of protoveratrine which causes a given fall in blood pressure varies from patient to patient, but in each patient, above a minimal dose, an increase in dose causes an increased effect in the dosage range studied. Larger doses cause greater fall in both systolic and diastolic blood pressure. Figure 2 shows the relation between the dose of protoveratrine in micrograms per kilogram and maximum fall in mean pressure (one-half the sum of the sys-
tolic and diastolic pressure) in 6 hypertensive patients.

In general, doses of 1 microgram per kilogram, or less, have little or no effect. Above this level and up to 3 micrograms per kilogram there is an increased response with increasing doses. Larger doses have not yet been tested.

Cardiodecelerator Action. The fall in blood pressure is accompanied by a decrease in heart rate. This is a sinus bradycardia of vagal origin and can be abolished by atropine. Figure 4 illustrates the response to a dose of protoveratrine in a patient with essential hypertension and compares it to the response when the same dose is given simultaneously with sufficient atropine to produce an acceleration in pulse rate. Although the fall is somewhat less than with protoveratrine alone, a striking fall in both systolic and diastolic blood pressure occurs despite the concomitant increase in heart rate. Thus bradycardia is not essential for the vasodepressor effect. In some patients the simultaneous administration of atropine produces a more gradual fall of blood pressure. In 2 patients, administration of atropine during the hypotensive phase produced a transient

Fig. 1.—The response to the same dose of protoveratrine on five separate occasions in S.E., a 50 year old woman with essential hypertension. Weight 64.5 kilograms.
return to the original hypertensive level during the period of tachycardia.

*Cold Pressor Test.* The response to the cold pressor test is not abolished during the hypertensive period following administration of protoveratrine. However, in 8 of 10 patients examined the rise in pressure produced by immersing the hand in cold water during the hypotensive period was much below the usual resting blood pressure of the patient. For example, a patient whose blood pressure rose from 176/116 to 214/138 with the cold pressor test had a rise of only 126/80 to 146/84 after the intravenous administration of protoveratrine;
Fig. 3.—The effect of erect posture before and after protoveratrine. N.P., a 46 year old man, and S.E., a 50 year old woman, both had essential hypertension. The solid black areas represent the blood pressure with the patients in the erect position; all other lines represent values found with the patients recumbent. The hatched areas represent the duration of the subjective warmth after intravenous injection of protoveratrine. In the graph of N.P. is also illustrated the response of hypertensive headache to the hypotension induced by protoveratrine (+ + +, severe headache; 0, no headache; ±, intermittent headache).

Fig. 4.—The response to protoveratrine and protoveratrine with atropine
another had a cold pressor response of 166/114 to 210/142 before and 116/78 to 130/100 after protoveratrine.

Effect of Erect Posture on Blood Pressure and Heart Rate. In more than half of forty experiments a moderate postural hypotension occurred, affecting the systolic level more than the diastolic. It did not differ much from the postural response before the drug was administered. In some patients, assumption of the erect position led to a more profound diastolic as well as systolic fall in pressure, particularly at the time of maximum action of the protoveratrine. Postural hypotension was always associated with an increase in heart rate (fig. 3).

Subjective Sensations. In every instance the intravenous administration of a large enough dose of protoveratrine produced a subjective sensation of marked warmth in the face, mouth, throat, hands, epigastrium, perineum, and feet, which was not unpleasant. The intensity of this warm feeling, its extent, and its duration of action (ten to twenty-five minutes) were proportional to the dose (fig. 3). It appeared sooner than the first change in blood pressure, was most marked during the period of rapid fall, and waned thereafter until it was completely gone before any marked rise in blood pressure towards previous hypertensive levels could be observed. The areas of most intense warmth seem to be those areas most richly supplied with sensory nerves. This sensation of warmth was not accompanied by flushing. In six instances sweating on the forehead was noted.

With the highest doses given, which varied in different patients from 0.12 to 0.20 mg., there was frequently slight dizziness during the period of warmth. This was aggravated by quick motions of the head or eyes but was only apparent when the subject's eyes were open and was transient, lasting only as long as the warm sensation. It appeared in 9 patients, eleven times as a slight light-headed feeling and nine times as definite dizziness. It is probable that large enough doses will produce this symptom in any patient. In 5 patients on eighteen occasions large doses caused a pressing, choking sensation in the epigastrium and sub-sternally with a tendency towards deep, sighing respirations. The question naturally arises whether this symptom is due to myocardial ischemia. Of the 2 patients in the series with angina pectoris neither experienced this substernal oppressive feeling after intravenous protoveratrine despite falls in blood pressure from 210/120 to 108/74 and 184/120 to 106/76. This sensation of pressure usually lasted about ten minutes, occasionally fifteen minutes, and was most marked during the period of rapid fall in pressure. Nausea was noted thirteen times by 6 patients. It was of slight intensity nine times and of significant degree four times. Vomiting was not observed.

Although the administration of protoveratrine is attended by these subjective sensations, it may abolish other sensations presumably due to the hypertension. Five patients were given protoveratrine while suffering from headache. In one there was no response; in 2 there was mild relief attending the fall in blood pressure; in 2 (as in fig. 3) a severe headache was completely alleviated during the hypotensive period. It recurred intermittently as the level of the blood pressure rose somewhat and returned in its original intensity when the blood pressure approached initial levels.

T-Wave Changes. Many reports give the return of an inverted T to upright as evidence of a salutary effect of a particular antihypertensive program (sympathectomy,19 "rice diet",20 Vertavis5). Electrocardiograms made before treatment are compared with those made several months after treatment. In our experiments four of eight patients who had the pattern of left axis deviation with flat or inverted T had reversion of T to upright during the period of lowered pressure and a return of the upright T wave to a flat or inverted wave as the effect of the drug wore off and the blood pressure rose towards previous levels. This was observed twenty-eight times, usually in the dosage range of 0.10 to 0.12 milligram. Figure 5 illustrates a typical response. Administration of protoveratrine produced these changes only when a good hypotensive response was obtained.

Cardiac Arrhythmias. Doses of protoveratrine of the order of 3 micrograms per kilogram (or 2 micrograms per kilogram in patients whose resting pulse rate is 60, or less) may produce
transient cardiac arrhythmias. The first change is marked sinus bradycardia which may be followed by first-degree heart block or complete block with nodal rhythm. In the 168 trials, first-degree heart block occurred four times, nodal rhythm twelve times, ventricular extrasystoles twice, bigeminy twice, and Wenckebach phenomenon twice in 10 patients, of whom 4 were digitalized. When these arrhythmias appear, they are usually intermittent. Runs of regular rhythm alternate with runs of prolonged P-R interval or nodal beats.

The arrhythmias appear about ten to fifteen minutes after injection and usually last a few minutes. If the dose which produces arrhythmia is given simultaneously with atropine, no arrhythmia appears; yet, a blood pressure fall still occurs, although of lesser degree. That atropine can abolish the arrhythmia once it is established was illustrated by an experiment in which a slow heart rate, induced by 0.16 mg. of protoveratrine intravenously, was associated first with prolonged P-R interval and then with 2 to 1 heart block. A subcutaneous injection of 0.8 mg. of atropine sulfate caused the appearance of Wenckebach phenomenon, then regular rhythm with P-R = 0.28 second and, a few minutes later, regular rhythm with normal P-R interval.

Patients who are fully digitalized may show electrocardiographic changes, such as increased P-R interval or bigeminy at lower doses of protoveratrine. In one fully digitalized patient, administration of 0.1 mg. intravenously produced a P-R interval of 0.4 second which lasted over two hours, whereas other patients have received almost twice that amount without arrhythmia. A patient with auricular fibrilla-

![Fig. 5.-Changes in the T-wave after protoveratrine. The patient, J. F., a woman 49 years of age, had essential hypertension.](http://circ.ahajournals.org/)

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As in the anesthetized dog, the vasodepressor and cardiodecelerator action could be obtained by small intravenous doses. However, the response lasted only several minutes and was of only moderate degree. It was almost always attended or preceded by disagreeable side effects. Doses of 0.1 mg. produced only the peculiar subjective warmth and taste simi-
lar to that experienced after protoveratrine injection. Intravenous doses of 0.2 mg. provoked transient irregular respirations or even severe spasmodic coughing associated with a tight, choking feeling in the throat. In some instances a pressor response was observed.

Larger doses, up to 2.2 mg., were given intramuscularly, usually in divided doses. There were no disturbances of respiration. Only slight or no fall in blood pressure or heart rate occurred at doses that produced nausea, vomiting, and sweating except in one patient in whom there was a marked fall in pressure from 240/110 to 120/80 and a decrease in heart rate from 80 to 52. This was accompanied by nausea, vomiting, sweating, and apprehension. Atropine abolished the bradycardia but did not affect either the hypotensive response or the nausea and vomiting.

**Discussion**

These studies have borne out the supposition that individual veratrum alkaloids may be found which in a dosage range causing satisfactory clinical circulatory effects have insignificant side effects or none at all. Protoveratrine is such an alkaloid and it is possible that other ester alkaloids may be found which are as suitable or even better for clinical use than protoveratrine.* It is obvious that the ester alkaloid veratridine does not belong to this group and scarcely warrants further clinical trial.

The difference in toxicity between the two substances raises an important pharmacotherapeutic problem. The absolute toxicity, even if it is very high, does not in itself exclude a substance from those with potential clinical usefulness, provided the therapeutic efficacy is correspondingly high. Thus, protoveratrine with its high toxicity has also a high therapeutic efficacy, while veratridine which in the toxicity tests referred to was only one-tenth as toxic as protoveratrine, nevertheless, is clinically useless because its therapeutic efficacy is within the dosage range leading to severe side effects.

The upper range of the dosage of protoveratrine for therapeutic application is not yet definitely established. It should be remembered that protoveratrine is an exceedingly potent drug, and it is prone to lead to severe toxic effects if the therapeutic range is carelessly transgressed. Increasing the dose beyond a certain low range, in order to obtain greater effect, is as likely in the human as in the laboratory animal not to give better results. It is the relatively low effective dosage range employed in this study which is most apt to show reflex hypotensive action exclusively.4

The chemical relation to the cardiac glycosides has its parallel in the pharmacologic action upon the mammalian heart. It consists not only in an improvement of contractility of the failing heart by appropriate doses of protoveratrine but in toxic effects by larger doses on impulse conduction and generation of impulses similar to those caused by the cardiac glycosides. The observations presented above suggest that the action of the cardiac glycosides and the action of the veratrum alkaloids on the heart may be additive; hence special care is needed in gauging the dose in a patient who is under the influence of cardiac glycosides.

**Conclusions**

Protoveratrine and veratridine, two pure veratrum alkaloids, have been administered to human beings with hypertension. Protoveratrine can produce a significant fall in blood pressure lasting one to three hours at doses free of serious side effects. It causes a decrease in heart rate occurring simultaneously with the blood pressure fall. This can be annulled by atropine without, as a rule, abolishing the vasodepressor effect. The effects of posture and cold pressor test have been described. An inverted or flat T wave in Lead I in the electrocardiogram may revert to upright during the hypotensive period. Veratridine has an effect of similar nature but of shorter duration. It is less potent than protoveratrine and clinically useless because the dosage range leading to serious side effects is identical with, or even lower than, the range of therapeutic dosage.
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