Plants and the Heart

The veratrum alkaloids, eclampsia of pregnancy, and hypertension

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Veratrum is the generic name of 45 species of plant, for example, *Veratrum viride* (American green hellebore; false hellebore; Indian poke) *(Figures 1, and 2 [next page])*, and *Veratrum album* the white hellebore of Europe where it grows on alpine meadows. The name hellebore is misleading because the genus *Helleborus,* as for example the Christmas rose *H niger,* the black hellebore, is in the family Ranunculaceae. The genus veratrum is in the lily family (Liliaceae) and the species are mostly found in North America. For centuries it had been well known as a poisonous plant producing very unpleasant symptoms, especially purging, vomiting, and fainting, while sometimes severe prostration and death resulted from eating the rhizome. In 1819, William Brande of London wrote "Although it has been prescribed in some cases of mania and of epilepsy modern practitioners reject it."[1] Likewise, in the United States it was said in 1840 that "*Veratrum viride* has seen its day, that its glory has departed"[2]

However, the preparation and sale of a tincture of *V viride* by Dr Norwood of South Carolina in 1852 led to renewed interest in the medicine, which was found to "reduce the heart's action" and slow the pulse. It became

Figure 1. Veratrum viride. ***Author's collection.***

widely used to control the circulation in inflammatory diseases such as typhoid fever.

However, the really important use of this plant was discovered in the small town of Eufala in Alabama by Dr Paul DeLacy Baker in 1859, and this was for the treatment of eclampsia of pregnancy. In his paper "Veratrum Viride in chorea and other convulsive disorders," Dr Baker tells in graphic language how he had to manage a desperately ill woman who was having a succession of convulsions before and after the birth of her stillborn child. He told how he treated a severe convulsion, her seventh, after delivery:

> I immediately gave her fifteen drops of *Veratrum Viride* and directed that she should take ten more in two hours. There occurred no more convulsions and the woman recovered perfectly, she was not even nauseated though the medicine was given at regular intervals during the whole night.

He refrained from giving it before delivery for fear of harming the fetus. One might ask why did he use this remedy? The answer is given in his paper in which he tells of using it with success a year previously in a man who was clearly having an attack of grand mal epilepsy. In both cases he was treating a convulsion and he had no way of knowing that they had totally different causes. Dr Baker declared that "it is eminently a nervine."[2] At that time the term eclampsia was used for any type of fit or convulsion, and was not restricted to pregnancy.

Quite remarkably, that single report was the beginning of the use for nearly 100 years of veratrum in eclampsia and later in preeclampsia of pregnancy. It was known then that it "softened the pulse," but it would be another 48 years before the blood pressure could be accurately measured and certainly there was no concept of hypertension in pregnancy. Dr Norwood spoke of it as "a controller of vascular and arterial excitement" and Dr Baker wrote, "…by its influence, the heart's action is simply held in check, and the force of the circulation reduced to nature's standard." It was much better, said Dr Baker, than venesection—which was at the time the preferred treatment, usually in large and repeated amounts, for almost any serious disease.[2]

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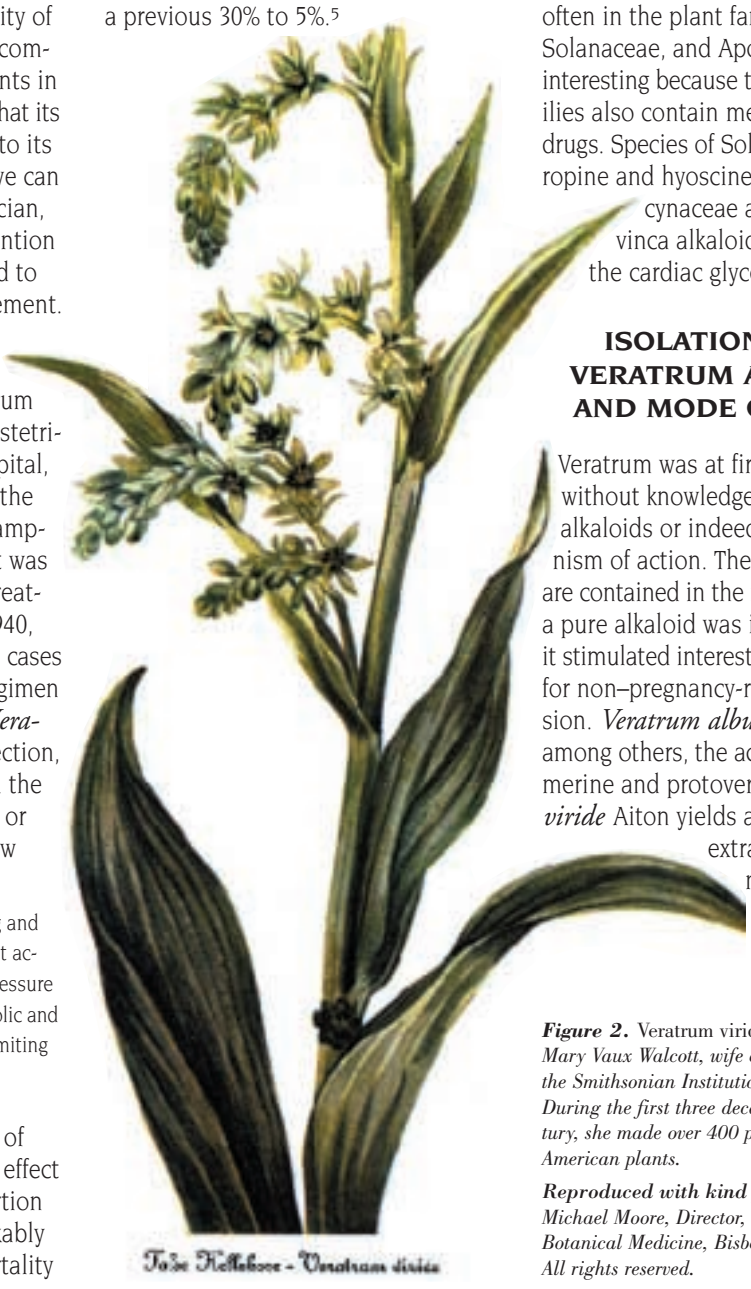
Experience in the United States with veratrum led to its use in Europe, and in fact the first large series and one in which the blood pressure was reported for the first time came from Professor Mangiagalli in Milan in 1907.[3] He noted that not only was the systolic blood pressure always very high in eclampsia, but that a fit was preceded by a strong increase, up to 280 mm Hg. In his clinic, an extract of *Veratrum viride* was given in preeclampsia whenever the pressure exceeded 150 mm Hg and in 94 women there was a mortality of only 6.3% over a 10-year period compared with 23% of his own patients in the 10 previous years. He wrote that its efficacy was most probably due to its hypotensive action. In passing we can note that it was an Italian physician, Scipione Riva-Rocci, whose invention of the pneumatic cuff in 1896 led to reliable blood pressure measurement.

Nevertheless, it was in the United States that the banner for veratrum therapy was kept aloft by the obstetricians at Cincinnati General Hospital, where it became established as the treatment of first choice for eclampsia of pregnancy, and, in 1935, it was said to have been the basis of treatment there for many years. In 1940, Bryant and Fleming reported 120 cases treated at that hospital with a regimen consisting of a preparation of *Veratrum viride,* "Veratrone," by injection, repeated every 15 minutes, until the pulse rate was below 60 mm Hg or the systolic blood pressure below 120 mm Hg. They wrote,

> The effect of an injection is startling and may cause undue alarm to those not accustomed to seeing it. The blood pressure falls sometimes to as low as 50 systolic and the heart beat to 40 per minute. Vomiting is copious.

It was combined with injections of magnesium sulfate, so the total effect of treatment is difficult to apportion to either drug, but it was remarkably effective in an era when the mortality rate could be as high as 20%. Only 2 of their patients died (1.67%), both from late sepsis, but 28% of the babies were stillborn.[4] The methods at Cincinatti were adopted in 1947 by Frederick Irving at the Boston Lying-In Hospital. He gave Veratrone subcutaneously, together with magnesium sulfate, to all of his patients who had convulsions, if necessary at 20-minute intervals, to keep the systolic blood pressure below 150 mm Hg. As a result, the death rate was reduced from a previous 30% to 5%.[5]



CHEMISTRY OF VERATRUM

Steroidal alkaloids are compounds with a fairly complex nitrogen-containing nucleus, and they are divided into two main classes: (i) the veratrum type with over 50 alkaloids and divided into two main subtypes, jerveratrum and ceveratrum—to give one example, the chemical formula for protoveratrine is C32 H51 O9 N; (ii) the solanum type, found in the Solanaceae family. The steroidal alkaloids are found most often in the plant families Liliaceae, Solanaceae, and Apocynaceae**.** This is interesting because these last two families also contain medically important drugs. Species of Solanaceae yield atropine and hyoscine, while from Apocynaceae are derived the vinca alkaloids, reserpine, and the cardiac glycoside ouabain.

ISOLATION OF THE VERATRUM ALKALOIDS AND MODE OF ACTION

Veratrum was at first used clinically without knowledge of its constituent alkaloids or indeed of their mechanism of action. The active principles are contained in the rhizome and when a pure alkaloid was isolated in 1944, it stimulated interest in using veratrum for non–pregnancy-related hypertension. *Veratrum album* L. contains, among others, the active alkaloids germerine and protoveratrine. *Veratrum viride* Aiton yields a potent stable extract containing a mixture of amorphous alkaloids, which was market-

Figure 2. Veratrum viride. *Painting by Mary Vaux Walcott, wife of the then director of the Smithsonian Institution Charles D. Walcott. During the first three decades of the 20th century, she made over 400 paintings of North-American plants.*

ed under the trade name of Veriloid. A related species from Mexico called *Schoenocaulon officinalis* A. Gray, known as Sabadilla, contains veratridine and cevidine and an extract of the plant is known as veratrine. Like the other two it is also a species of Liliaceae.

The three major effects of the veratrum alkaloids are hypotension, bradycardia, and vomiting. As long ago as 1597, the London surgeon John Gerard wrote in his famous herbal, "The root of white hellebor procureth vomite mightily wherein consisteth his chiefe vertue" *(Figure 3).*[6] However, it was Albert von Bezold, in 1867, who made the first scientific study, and his conclusion that the hypotension is due to afferent impulses from the heart producing a reflex fall of blood pressure has stood the test of time. Later work gave more detail. Veratrum causes the afferent impulses from the heart (the von Bezold reflex) and also from the lungs to discharge continuously, leading to arteriolar dilatation in skeletal muscle and the splanchnic area, with no fall in cardiac output. The decrease in peripheral resistance is caused through the sympathetic nervous system, as the drug does not increase blood flow in a sympathectomized limb. It is mediated through reflex inhibition of central vasoconstrictor impulses. Importantly, the alkaloids are not sympatholytic, and as a result the pressor reflexes such as the Valsalva maneuver are maintained and postural hypotension does not occur.[7]

TREATMENT OF HYPERTENSION

Sixty years ago, there was little that could be done to lower the blood pressure in patients with essential or renal hypertension. Potassium thiocyanate, introduced in 1901, was of minor value and the enthusiasm for lumbodorsal sympathectomy in the 1940s mirrored therapeutic desperation. The introduction of the ganglion-blocking drugs pentamethonium halide and hexamethonium halide in 1948 was an important advance, and at much the same time, physicians such as Edward Freis in Boston, USA, were attracted to the veratrum alkaloids, often in the form of Veriloid. When given orally, their hypotensive effect reached a maximum in 4 hours and had disappeared by 14

Figure 3. *Woodcut of* Veratrum album, *white hellebore, from Gerard's Herbal of 1597.*[6]

Reproduced from reference 6: *Gerard J.* The Herball or Generall Historie of Plantes. *London, UK: John Norton; 1597.*

hours. Freis and Stanton treated 40 patients with Veriloid for up to 13 months and found that the development of side effects and changing sensitivity to a given dose limited its usefulness. However, short-term treatment for a hypertensive crisis was very effective.[8]

Kauntze and Trounce, in 1951, reported 10 patients at Guy's Hospital all with a diastolic pressure over 120 mm Hg. Blood pressure control with oral Veriloid was good in 8, but its short-lived effect made control variable. Nausea was invariable, but usually mild *(Figures 4 and 5, page 232).*[9]

One of the best studies came from Doyle and Smirk in New Zealand in 1953, using the pure alkaloids neogermitrine and protoveratrine, and also mixed alkaloidal preparations. They achieved good blood pressure control in 15 out of 65 hypertensive patients. They found that although control was initially good in a majority, the margin between therapeutic and toxic doses narrowed as treatment is continued. The toxic manifestations were burning sensation in the mouth, hiccough, salivation, nausea, and vomiting. This study made it clear that the veratrum alkaloids, whatever the preparation used, were never going to be a satisfactory method of treating hypertension.[10]

At the time this was a disappointment because the mode of action with preservation of pressor reflexes and no postural hypotension was in marked contrast to the inhibition of these reflexes with ganglion-blocking agents.

SEVERE TOXICITY AND POISONING

The poisonous nature of veratrum had been known for centuries, and early settlers in North America used it as an insecticide and to poison crows. In Germany, it was used as an ointment to treat scabies, hence the name "Kratzwurzel," itch-root. Toxicity was an especial problem in earlier times when the potency of a plant extract would be unknown, a problem referred to by William Withering when he investigated the use of foxglove in cardiac failure in 1775. Dr Baker had found this, "soon after entering upon the practice of medicine." He was treating a lady with a high fever when she suddenly collapsed, "with an icy coldness which simulated the chill of death itself. Friends and relatives were hurried for to see her die." Yet she recovered, with a soft, slow, and regular pulse.[2] The use of the pure alkaloids or standardized extracts after 1944 helped to reduce severe side effects.

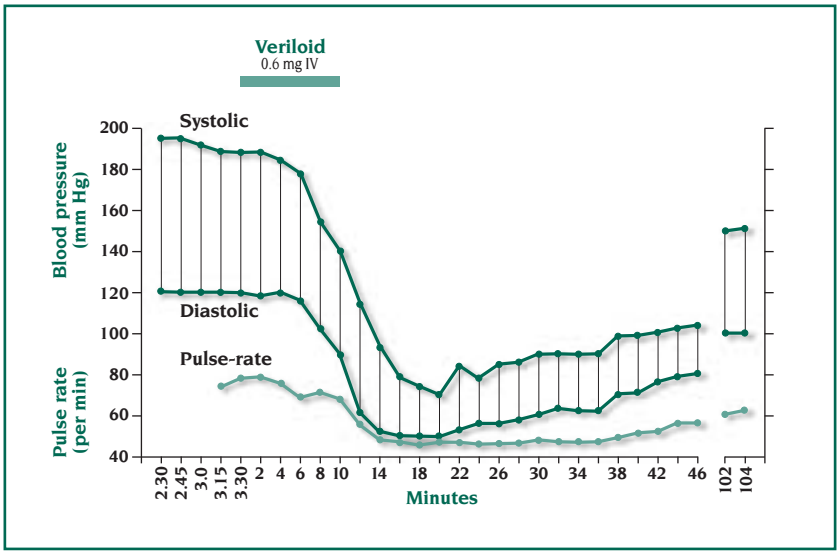


Figure 4. *Effect of intravenous Veriloid* (Veratrum viride) *in a 39-year-old man with essential hypertension. Blood pressure falls to 70/50 mm Hg and pulse rate to 46 per minute at 20 minutes.*

Reproduced with permission from reference 9: *Kauntze R, Trounce J. The hypotensive action of Veriloid* (Veratrum viride)*. A clinical investigation.* Lancet. *1951;1:549-555. Copyright © 1951, Elsevier.*

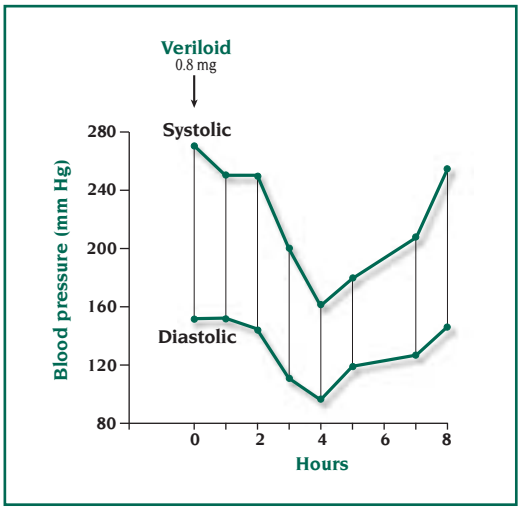


Figure 5. *Extent and time scale of blood pressure reduction with Veriloid* (Veratrum viride) *by mouth in a 19-year-old man with malignant renal hypertension. Blood pressure fall is maximal at 4 hours and returns to near the control level at 8 hours.*

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A different problem, that of plant identification, led in 1985 to a report of accidental poisoning in France, when five men were taken ill after making wine from what they thought was yellow gentian, *Gentiana lutea* L. It was in fact *Veratrum album.* They all had vomiting, abdominal pain, hypotension, and bradycardia and in one there was complete atrioventricular block with idioventricular rhythm, which recovered without pacing. When not in flower these two species can be readily confused.[11] It is known to be a strong teratogen, and it has been reported that ewes who eat it may have a lamb with a central eye.[12]

COMMENT

The veratrum alkaloids have a very attractive mode of action in hypertension and were it not for their inevitable side effects they might constitute a good form of treatment today. Variable response is also a problem, not due apparently to tachyphylaxis. Unfortunately, the toxicity, especially the vomiting, seems to be linked directly to their mode of action via the von Bezold reflex and this almost rules them out for long-term therapy. This problem does not, however, apply to short-term treatment, as in preeclampsia and eclampsia, but modern drugs such as methyldopa and labetalol have overtaken veratrum for this condition. However, it is clear that Dr Paul DeLacy Baker initiated a major advance in the treatment of eclampsia of pregnancy when, no doubt at his wit's ends to know what to do, he treated that woman in 1859. The large series of preeclampsia and eclampsia reported in the first half of the 20th century leave one in no doubt that veratrum was a life-saving drug and furthermore that it could be administered with safety, especially now that blood pressure measurement had become readily available.

As one might expect, the distribution of effective medicines within the plant kingdom is not predictable because plant medicines are secondary compounds within plants, which have evolved chiefly to protect them from predators. However, it so happens that the Liliaceae family does have another genus with medicinal properties. This is the Mediterranean sea onion or squill, *Drimia maritima,* used in former times to treat heart failure. It contains cardiac glycosides, and oxymel of squill was invented by Pythagorus as an expectorant.

The veratrum alkaloids have such an interesting and seemingly good mode of action that it seems a pity that side effects have limited their use for chronic administration. Perhaps an enterprising pharmaceutical company could either synthesize a derivative without the side effects, or else investigate some of the 40 or so alkaloids that may not so far have been studied pharmacologically.

I thank Dr Walter Sneader of the University of Strathclyde for his valued advice.

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