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Research Article

THE HEMODYNAMIC EFFECTS OF HYPOTENSIVE DRUGS IN MAN.[1] I. VERATRUM VIRIDE

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INTRODUCTION

Renewed interest in veratrum viride began with the investigations of Craig and Jacobs (1) who isolated the veratrum alkaloids and found them to be sterol compounds related chemically to the digitalis glycosides, the steroid hormones and vitamin D. Using the pure alkaloids, Krayer and his co-workers (2) demonstrated that sub-toxic doses in experimental animals produced a vasodepressor response of reflex nature. They found that the most important receptor area for the reflex was located in the left ventricle of the heart, and that the primary afferent pathway was the vagus nerve. They did not determine the efferent pathways of this vasodepressor response.

Meanwhile, clinical interest in veratrum viride steadily increased because of its therapeutic use in the eclamptic toxemias of pregnancy (3, 4) and, more recently, in cases of severe essential hypertension (5). Nevertheless, very little was known of its hemodynamic or other pharmacologic effects in human beings. The present study was undertaken to elucidate the actions of the drug in both hypertensive and normotensive individuals.

MATERIALS AND METHODS

The subjects were patients, mostly hypertensive, admitted to the Massachusetts Memorial Hospitals. Both oral (Vertavis [3]) and parenteral (Veratrone [4]) preparations of veratrum viride were administered. Arterial pressure was measured either with a Hamilton manometer (6) (during the determinations of vasopressor responses, cardiac output, and/or hepatic-portal blood flow); or with an arm cuff and a mercury manometer. Cardiac output was determined directly by the Fick principle using the intravenous catheter method of Cournand (7) and determinations of blood oxygen by the method of Van Slyke and Neill (8). In order to insure complete mixing, the venous blood samples were withdrawn always from the pulmonary artery, while oxygenated blood was taken either from the brachial or the femoral artery. Ballistocardiograms (9, 10) were recorded simultaneously in these and other hypertensive subjects but due to the abnormal ballistocardiographic complexes occurring in patients with hypertension, accurate measurements of cardiac output by this method were not possible. Blood flow in the forearm and calf was determined plethysmographically by the method of Wilkins and Eichna (11), modified by the use of a thin rubber sleeve instead of the rubber diaphragms cemented to the skin (12). Hepatic-portal (splanchnic exclusive of renal and adrenal) blood flow was estimated by the bromsulfalein method of Bradley *et al.* (13), with three modifications: first, peripheral blood samples consistently were arterial; second, determinations of BSP were made on oxalated plasma rather than serum; and third, estimations of blood flow rate were calculated for the times at which arterial blood samples were drawn. Renal plasma flow (PAH) and glomerular filtration rate (mannitol, inulin) were determined by the methods of Smith and his co-workers (14).

Vasopressor overshoots after blood-pressure-lowering procedures were measured by the method of Wilkins and Culbertson (15), reflex vasoconstrictions in the digits by the method of Bolton, Carmichael and Stürup (16) and skin temperature responses according to the method of Uprus, Gaylor and Carmichael (17). Vascular distensibility in the extremities was determined using the method of Litter and Wilkins (18).

RESULTS

I. *Cardiac function*

Cardiac output, mean arterial pressure and total peripheral resistance

Control and experimental determinations were carried out during a single test on five patients given Veratrone by intramuscular injection. In two other patients a control study was done, after

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[3] Irwin, Neisler & Company, Decatur, Illinois.

[4] Parke, Davis & Company, Detroit, Michigan.

TABLE I

Effects of veratrum viride on blood pressure, cardiac output and total peripheral resistance

Patient and diagnosis	Sex	Age	Drug and dose	Control					After veratrum					
				Mean arterial pressure	Cardiac rate	Cardiac output	Total peripheral resistance	Pulmonary arterial pressure	Time from administration of drug	Mean arterial pressure	Cardiac rate	Cardiac output	Total peripheral resistance	Pulmonary arterial pressure
				mm. Hg‡	*per min.*	*L. per min.*	*dynes cm.-5 sec.*	*mm. Hg*	*minutes*	*mm. Hg*	*per min.*	*L. per min.*	*dynes cm.-5 sec.*	*mm. Hg*
W. G. Essential hypertension	M	52	Vertavis* 40 Craw units	166.5 167.5	92 97	6.66 6.44	2010 2040	32/15 30/18	232 244	119 130	86 88	7.30 6.70	1302 1483	21/16 21/14
E. S. Essential hypertension	F	46	Vertavis 40 Craw units	185.5 183	112 108	6.21 5.36	2394 2730	26/8 23/7	110 120	135 141	94 93	6.94 5.60	1557 2012	18/8 19/8
S. B. Essential hypertension	M	48	Veratrone† 1.0 cc.	162.5	84.5	5.83	2227	21/7	34 94	146 158.5	77 79	6.10 6.24	1912 2031	18/5 21/8
J. Mc. Essential hypertension with cardiac failure	M	52	Veratrone 1.0 cc.	225 218	139 133	4.22 4.28	4210 4075	95/62 87/60	38 74	177 174	108 106	4.95 5.57	2855 2500	55/26 60/30
M. H. Essential hypertension	F	49	Veratrone 0.6 cc.	190	86	5.75	2640	25/8	82	166.5	73	5.01	2660	23/9
W. C. Malignant hypertension with cardiac failure	M	50	Veratrone 0.4 cc.	175 180	82 82	3.98 3.77	3460 3820	65/36 69/36	11 13	154 138	78 63	4.39 4.94	2800 2200	66/34 41/20
J. C. Malignant hypertension with cardiac failure	M	48	Veratrone 0.45 cc.	166.5 165.5	97 94	5.98 5.47	2220 2420	46/22 37/19	17 27	159.5 157	90 85	5.80 5.16	2190 2420	27/10 22/4

* Oral veratrum viride given twice per day for one week after control test in four equal hourly doses (time counted from beginning of last dose).
† Parenteral—given intramuscularly immediately following control period.
‡ Determined by planimetric measurement of the arterial pulse waves.

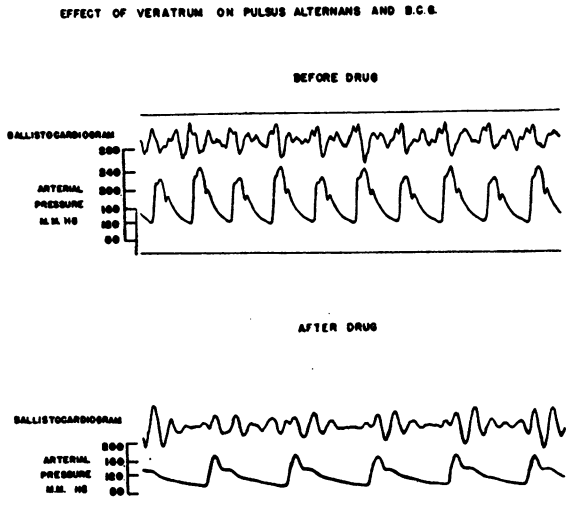

FIG. 1. OPTICAL RECORDS OF THE BALLISTOCARDIOGRAM AND THE BRACHIAL ARTERIAL PRESSURE (HAMILTON) BEFORE AND AFTER THE ORAL ADMINISTRATION OF 30 CRAW UNITS OF VERATRUM VIRIDE IN PATIENT M. A., MALE, AGED 43

Pulsus alternans was present in the control record. Following veratrum there was a marked reduction in arterial pressure, a disappearance of pulsus alternans, and a return of the ballistocardiogram to a more normal pattern.

which Vertavis was administered orally for one week before the determinations were repeated. The results in both types of experiments were essentially the same (Table I). In all but two of the seven cases there was a fall in mean arterial pressure of from 8 to 28 per cent, and in three patients, of more than 20 per cent. However, during the period of reduced blood pressure depression of cardiac output was not observed. Rather, in three cases, there was a slight increase in cardiac output of 6 to 8 per cent, and in two patients, with congestive heart failure, an increase of 20 and 24 per cent. As a result of the significant fall in mean arterial pressure and slight rise in cardiac output there was a considerable decrease in the calculated total peripheral resistance (between 30 and 35 per cent in four of the cases and of 11 per cent in one case). In two cases (M. H. and J. C., Table I) there were insignificant changes in cardiac output or peripheral resistance during the time the cardiac output determinations were being carried out, the major portion of the test period in patient M. H. having been devoted to estimations of hepatic-portal blood flow (Table III, Figure 5).

Other aspects of cardiac function

It was not unusual to observe a decrease in cardiac enlargement as measured by roentgenography (5) in patients who exhibited a prolonged reduction in blood pressure after months of continuous oral administration of veratrum viride. Less frequently, changes toward normal in the electrocardiogram were observed. Pulsus alternans usually decreased or disappeared during the reduc-

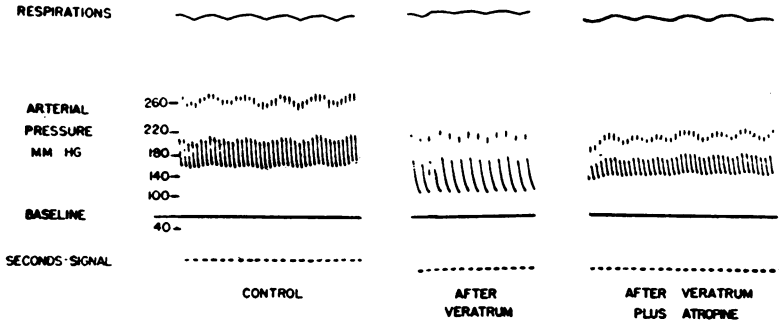

FIG. 2. OPTICAL RECORDS OF RESPIRATION AND BRACHIAL ARTERIAL PRESSURE (HAMILTON) IN PATIENT C. B., FEMALE, AGED 49

Ninety minutes following the oral ingestion of 20 Craw units of veratrum viride (second tracing) there was a fall in arterial pressure accompanied by bradycardia. Atropine (1 mgm. intravenously) was given immediately, and three minutes later (third tracing) there was a tachycardia and a rise in diastolic but not in systolic pressure. The diastolic rise was more apparent than real since it was associated with shortening of the run-off period.

TABLE II

Effect of veratrum viride (Veratrone) on blood flow in forearm and calf*

Case no.	Patient and diagnosis	Sex	Age	Dose	Control			After veratrone			
					Arterial pressure	Blood flow per 100 cc. limb volume		Time after drug	Arterial pressure	Blood flow per 100 cc. limb volume	
						Arm	Leg			Arm	Leg
					mm. Hg	*cc.*	*cc.*	*minutes*	*mm. Hg*	*cc.*	*cc.*
1	D. C. Essential hypertension	F	27	0.6 cc.	180/112 173/115 170/116	2.83 2.56 3.41	3.01 2.77 2.78	11 12 34 52 77 97 107 134	158/100 141/90 111/73 103/71 115/81 121/88 132/93 137/95	2.85 2.73 2.25 2.24 2.95 2.84 2.86 3.38	2.19 2.02 1.69 1.77 2.40 2.37 2.69 3.01
2	L. B. Essential hypertension	F	49	0.5 cc.	160/100 156/110	3.29 2.74	2.54 2.57	13 34 46 67	134/106 132/99 129/95 —	2.68 2.39 1.97 2.46	2.63 1.91 1.73 2.21
				0.15 cc. at 70 minutes				87 99 109	114/93 147/94 149/100	2.37 2.98 2.59	2.47 2.56 2.27
3	M. St. J. Essential hypertension	F	51	0.5 cc.	196/120 198/116	3.92 3.94 4.04	2.54 2.42 2.40	20	190/116	3.40	2.42
				0.2 cc. at 35 minutes				57 74 85	164/110 160/104 158/101	2.22 3.28 3.11	2.30 2.43 2.52
4	D. C. Essential hypertension	M	50	0.5 cc.	201/121 175/112	1.49 1.86	— —	50	181/113	2.18	—
				0.2 cc. at 55 minutes				72 97	179/110 156/107	2.76 2.48	— —
3	F. V. Chronic glomerulonephritis advanced renal damage	M	22	0.5 cc.	175/114 167/116	2.23 2.46	2.66 2.73	23 36	166/106 164/98	— 2.88	2.96 2.89
				0.15 cc. at 50 minutes				55 68 79 91	162/99 152/92 152/88 154/85	2.81 2.54 2.54 2.72	2.82 2.98 2.73 3.04
6	R. F. Essential hypertension advanced renal damage	M	46	0.75 cc.	199/130 186/122 189/120	1.70 2.10 2.16	3.29 2.86 2.76	13 25 39	193/120 170/109 136/88	2.49 2.50 2.16	3.08 2.82 2.27

* Parenteral—given intramuscularly immediately following control period.

tion of blood pressure following veratrum viride, and the ballistocardiogram also occasionally reverted toward a more normal form (Figure 1).

Pulmonary congestion lessened and dyspnea improved during the hypotensive action of veratrum. For example, patient J. Mc. (Table I) at the time of the control cardiac output determination exhibited clinical evidences of cardiac failure, including dyspnea and pulmonary congestion. After Veratrone, the systemic arterial pressure declined from 290/185 to 230/135 while the pulmonary arterial pressure fell from 90/60 to 58/28 mm. Hg and the cardiac stroke volume increased from 32 to 48 ml. At this time the patient noted subjective relief of dyspnea. The injection of Veratrone was followed by a decrease in pulmonary arterial pressure in the three cases who exhibited abnormal elevations (Table I).

Bradycardia was frequently observed after veratrum viride and was shown to be vagal in origin

by the fact that it could be abolished by the intravenous injection of 1 mgm. of atropine. Although atropine abolished the bradycardia it did not greatly affect the reduction in blood pressure (Figure 2). In occasional patients bradycardia was not manifested following Veratrum even though the arterial blood pressure was significantly reduced (case W. G., Table I). Thus, bradycardia appeared to be a common, perhaps an augmenting, but not a necessary accompaniment of the hypotensive response.

II. *Blood flow through various regions*

Blood flow through the forearm and calf

All six hypertensive patients who were studied plethysmographically following the intramuscular injection of Veratrone (Table II), had a decrease in mean arterial pressure of from 8 to 38 per cent. The blood flow to the forearm in two of the six subjects decreased as the arterial pressure fell, but returned to control levels as the arterial pressure became stabilized at a lower level. In three subjects, as the pressure fell the blood flow in the forearm increased and remained elevated, while in one the flow was unchanged. The blood flow in the calf followed a similar pattern, falling in two of five cases but returning to control levels before the blood pressure, increasing in two, and remaining unchanged in one. Since in all of these patients blood flow remained at or returned to or above control values during the hypotensive response to Veratrone a decrease in peripheral resistance in the limbs was assumed to have occurred.

Blood flow through the hepatic-portal circuit

The blood flow through the liver (EHBF) was estimated in three hypertensive patients in the basal state and horizontal position both before and after administration of veratrum viride (Table III). In the first patient, W. G., two separate studies were made, one for control measurements and the other after a week of treatment with Vertavis tablets by mouth. The latter study revealed an increase of 25 per cent in the average EHBF and a decrease of 27 per cent in the average "mean" $(=\frac{S+D}{2})$ arterial pressure, indicating a significant reduction in hepatic-portal vascular resistance.

In the two other cases acute experiments were performed. After a period of control observations, patient J. C. received 0.6 ml. of Veratrone solution intramuscularly. Twenty minutes later, because there had been no evidence of a hypotensive response, but on the contrary, a moderate pressor reaction, he received a dose of 0.2 ml. of Veratrone. Twelve minutes after the second injection, EHBF and arterial pressure had decreased from control values by 12 per cent and 32 per cent respectively, and at 22 minutes by 21 and 46 per cent respec-

TABLE III

Effects of veratrum viride on estimated hepatic blood flow

Patient and diagnosis	Sex	Age	Drug and dose	Control		After veratrum		
				Arterial pressure	EHBF	Elapsed time	Arterial pressure	EHBF
				mm. Hg	*ml. per min. per 1.73 sq. m.*	*minutes*	*mm. Hg*	*ml. per min. per 1.73 sq. m.*
W. G. Essential hypertension	M	52	Vertavis* 40 Craw units	235/142 230/140	1106 1307	282 293 306	183/95 177/90 145/90‡	1590 1411 1521
J. C. Essential hypertension	M	50	Veratrone† 0.8 cc.	219/121 215/120 213/120	1104 1269 1183	15 24 32 42	230/130 240/130 150/80 120/60	1126 1285 1040 931
M. H. Essential hypertension	F	49	Veratrone 0.7 cc.	220/133 224/141 220/135	925 1154 1243	15 31 42 54 60	210/120 183/105 177/106 184/110 185/112	1130 960 1129 1050 1260

* † Notations as in Table I.

‡ Clot in needle prevented accurate recording of arterial pressure.

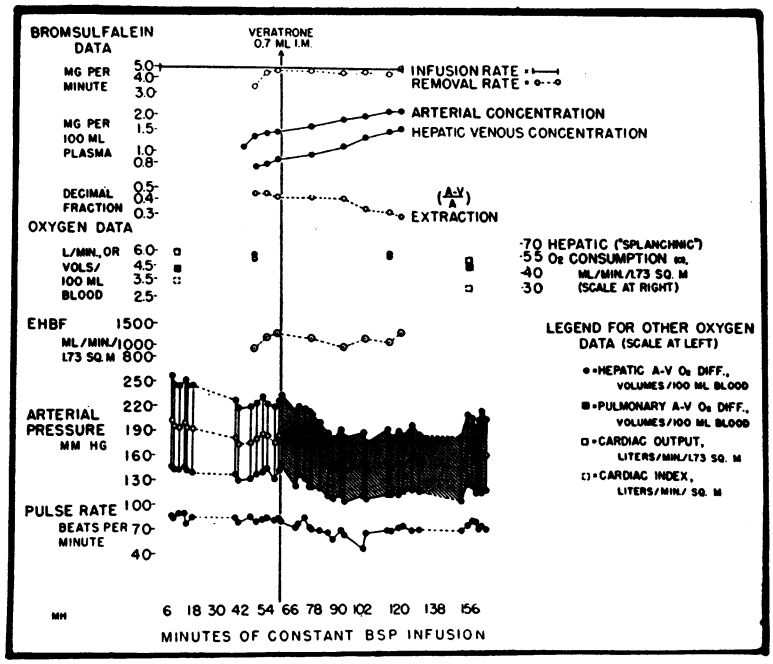

FIG. 3. CHART OF ESTIMATED HEPATIC-PORTAL BLOOD FLOW (EHBF), ARTERIAL PRESSURE (HAMILTON), AND PULSE RATE IN PATIENT M. H., FEMALE, AGE 50

Above are the infusion and removal rates, the arterial and hepatic venous concentrations and the extraction rate of bromsulfalein. In the middle are data on hepatic and pulmonary A–V oxygen differences, cardiac output (Fick), cardiac index and hepatic oxygen consumption. Observed data are represented by solid symbols and lines, calculated values by open symbols and lines. Following the injection of 0.7 ml. of Veratrone (vertical line) there was a significant fall in arterial pressure. The estimated hepatic blood flow fell off slightly during the first 30 minutes after the drug and then increased above the highest level recorded in the control period.

tively. Thus, a reduction in hepatic-portal vascular resistance became apparent, but the hypotensive reaction then became excessive, and proceeded to a state of collapse with arterial pressure of 90/48 mm. Hg, pulse rate of 75 beats per minute, and development of nausea and vomiting. Therefore, experimental observations were discontinued and restorative therapy was instituted. While this case illustrates acute hemodynamic changes strikingly, it serves also as an example of the effects of overdosage.

The third patient, M. H., was observed similarly before and after a single injection of 0.7 ml. of Veratrone, which in this instance proved to be less than the optimal therapeutic dose and produced only a modest reduction in arterial pressure (Table III, Figure 3). Nevertheless, EHBF remained above the lowest control value and finally rose above the highest control value at a time when "mean" arterial pressure had become stabilized at a level definitely (17 per cent) below the average control. Hence, this case also is consistent with the others in indicating that a significant reduction occurs in hepatic-portal vascular resistance following treatment with veratrum viride.

Blood flow through the kidneys

Changes in renal blood flow were similar to those observed in hepatic blood flow after veratrum viride. In two (W. G. and A. D.) of three cases maintained for one week on continuous oral administration of the drug (Table IV), the effective renal plasma flow increased moderately despite significant reductions in arterial pressure. In the

TABLE IV

Effects of veratrum viride on renal clearances

Patient and diagnosis	Sex	Age	Drug and dose	Control					After veratrum					
				Arterial pressure	Plasma clearance mannitol	Plasma clearance PAH	Filtration fraction	Urine flow	Time after drug administration	Arterial pressure	Plasma clearance mannitol	Plasma clearance PAH	Filtration fraction	Urine flow
				mm. Hg	*cc. per min. per 1.73 sq. m.*	*cc. per min. per 1.73 sq. m.*	*per cent*	*cc. per min.*	*minutes*	*mm. Hg*	*cc. per min. per 1.73 sq. m.*	*cc. per min. per 1.73 sq. m.*	*per cent*	*cc. per min.*
W. G. Essential hypertension	M	52	Vertavis* 40 Craw units	219/126		330			238	154/90	73	410	17.8	1.9
				215/132	142	367	38.5	2.2	282	183/95	71	369	19.2	1.6
				235/142	104	314	33.1	2.4	293	177/90	62	313	19.8	1.6
				230/140		306			306	145/90‡	72	414	17.4	1.6
D. W. Essential hypertension	F	38	Veratrone† 0.6 cc.	200/108	110	425	25.9	1.3	17	98/55	37	238	15.5	0.7
				208/105	104	422	24.7	1.2	29	94/60	33	256	12.9	0.5
				204/104	112	492	23.0	1.1	44	115/60	104	587	17.7	2.1
G. A. Essential hypertension	F	42	Veratrone 0.7 cc.						28	170/110	90	414	21.8	2.2
				214/126	132	487	27.2	9.4	48	165/105	87	382	22.8	1.7
									72	160/105	66	306	21.6	1.3
				218/128	122	441	27.6	7.4	89	165/108	100	443	22.5	1.8
S. B. Essential hypertension	M	48	Veratrone 1.0 cc.						10	228/118	124	370	33.5	7.2
				228/116	134	424	31.6	11.0	31	222/118	93	411	22.7	4.8
									51	228/116	66	358	18.4	4.1
				222/114		412		10.9	73	200/102	89	386	23.0	2.9
									92	216/110	73	373	19.6	2.3

TABLE IV—*Continued*

Patient and diagnosis	Sex	Age	Drug and dose	Control					After veratrum					
				Arterial pressure	Plasma clearance inulin	Plasma clearance PAH	Filtration fraction	Urine flow	Time after drug administration	Arterial pressure	Plasma clearance inulin	Plasma clearance PAH	Filtration fraction	Urine flow
				mm. Hg	*cc. per min. per 1.73 sq. m.*	*cc. per min. per 1.73 sq. m.*	*per cent*	*cc. per min.*	*minutes*	*mm. Hg*	*cc. per min. per 1.73 sq. m.*	*cc. per min. per 1.73 sq. m.*	*per cent*	*cc. per min.*
G. J. Chronic glomerulonephritis	M	47	Veratrone 0.7 cc.	192/120	65	285	20.1	8.3	13	170/112	40	141	24.6	2.7
				188/118	57	296	17.1	7.4	25	178/110	67	202	29.2	1.4
									46	150/90	64	204	27.3	0.8
									66	148/88	62	243	22.2	0.6
									90	150/90	75	283	23.0	0.7
									116	162/94	97	366	23.7	0.8
F. V. Chronic glomerulonephritis	M	22	Veratrone 0.7 cc.	190/130	44	204	19.7	2.8	6	180/125	23	122	17.6	1.0
				187/132	38	135	25.8	2.3	16	164/102	28	119	21.4	0.7
				190/134	28	128	20.2	1.3	38	160/90	25	117	19.7	0.6
									57	155/100	29	155	17.3	0.7
									86	146/95	48	228	19.3	0.8
E. S. Essential hypertension	F	44	Veratrone 0.6 cc.	190/95		380		5.1	8	195/92	86	375	22.9	1.4
				194/90	109	454	24.0	5.0	18	170/78	63	266	23.7	0.3
				200/95	124	496	25.0	3.1	28	160/72	65	350	18.6	0.3
				200/95	130	542	24.0	2.5	43	140/68	63	294	21.4	0.2
									51	136/68	109	640	17.0	0.4
									66	140/72	105	630	16.7	0.4
M. G. Essential hypertension	M	49	Veratrone 0.6 cc.	212/116	116	568	20.5	9.4	10	205/125	66	275	24.8	1.6
				190/116	108	416	25.6	4.0	30	140/95	87	375	23.0	0.3
				190/116	112	485	23.0	2.5	60	164/100	105	590	17.8	0.7
B. H. Chronic glomerulonephritis	M	52	Vertavis* 35 Craw units	230/114	43	147	34.2	8.4	70*	190/86	23	143	16.1	2.6
				226/116	50	141	38.2	7.1	82	190/88	29	133	21.9	2.5
				226/116	37	126	34.1	7.2	92	180/86	28	138	19.2	2.4
A. D. Essential hypertension	F	68	Vertavis* 30 Craw units	188/104	53	342	18.0	4.3	110*	116/68	57	322	17.8	3.3
				186/102	47	238	21.4	2.5	121	124/74	74	416	17.7	4.0
									131	130/76	50	263	18.9	2.6

* † Notations as in Table I.
‡ Notation as in Table III.

third (B. H.) it remained unchanged. In all of seven cases who received veratrum viride acutely by intramuscular injection (Table IV) there was an initial decrease in renal plasma flow followed in the later period by a return to control values. In five of these cases renal blood flow after veratrum rose to levels above those recorded in the control period (Figure 4, Table IV).

Estimations of cardiac output, hepatic-portal and renal blood flows were carried out in a single subject (case W. G., Tables I, III and IV) both before and after one week of treatment with orally administered veratrum viride. Following the cardiac output determinations the intravenous catheter was moved from the right pulmonary artery to an hepatic vein, urine samples being obtained meanwhile through a bladder catheter. These procedures permitted estimation of the percentage of the cardiac output circulating through the hepatic-portal and renal vascular beds before and after veratrum viride. In the control period the mean cardiac output was 6.55 L. per min., the average estimated hepatic-portal blood flow was 1.2, and the mean renal blood flow was 0.565 L. per min. After one week of continuous oral administration of veratrum viride the mean values were for cardiac output 7.0 L. per min., for estimated hepatic-portal blood flow 1.48 L. per min., and for renal blood flow 0.612 L. per min. Thus, estimated hepatic-portal blood flow utilized 18.3 per cent of the cardiac output before the drug and 21.7 per cent after the drug; renal blood flow utilized 8.6 per cent of cardiac output prior to treatment and 8.7 per cent after treatment. These results suggest that despite a reduction in arterial pressure from approximately 225/130 to 170/92 the percentage of the cardiac output utilized by the hepatic-portal and renal vascular beds showed no significant change.

III. *Renal function*

In addition to the studies of renal plasma flow just described, measurements of glomerular filtration, filtration fraction and urine volume were also made (Table IV). Four of the patients exhibited advanced renal disease characterized by abnormally low clearances of inulin and para-aminohippurate.

Mannitol clearance following veratrum appeared to fall and remain low. Inulin clearance

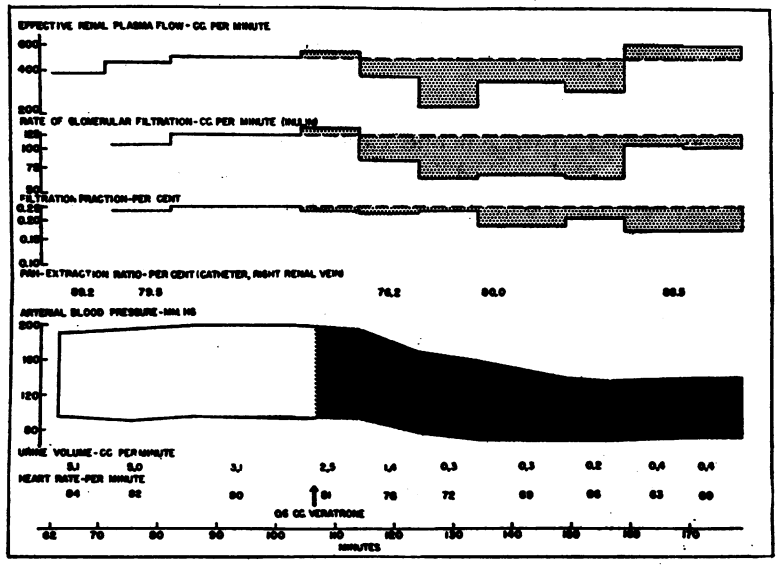

FIG. 4. CHART OF RENAL PLASMA FLOW, GLOMERULAR FILTRATION RATE, FILTRATION FRACTION, RENAL EXTRACTION OF PAH, BRACHIAL ARTERIAL PRESSURE, URINE VOLUME AND HEART RATE BEFORE AND AFTER INTRAMUSCULAR VERATRUM IN PATIENT E. S., FEMALE, AGED 44

Oliguria appeared early, and remained marked even when the renal clearances had returned to control levels. Note relatively constant extraction of PAH.

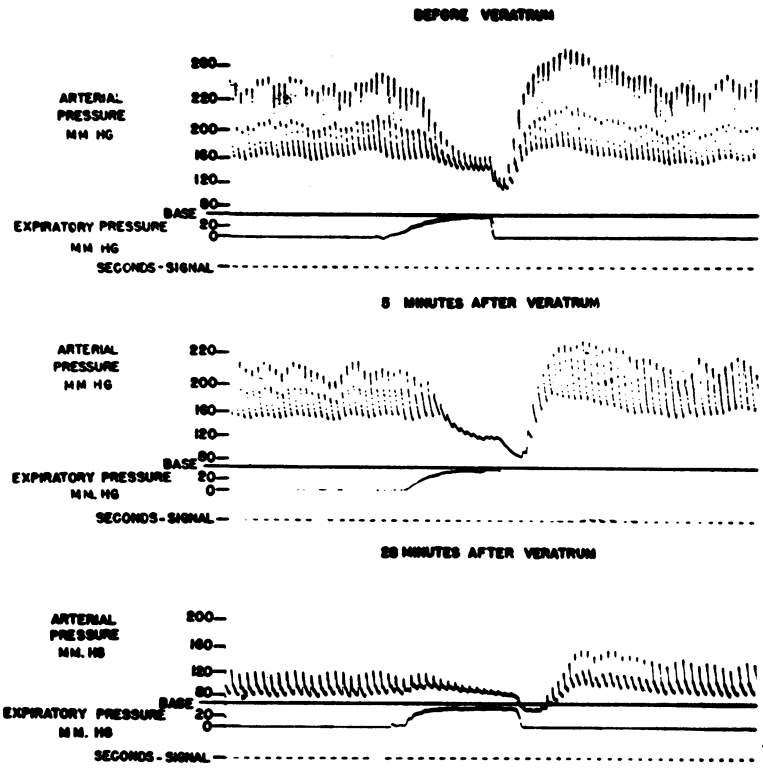

FIG. 5. OPTICAL RECORDS OF THE RESPONSE IN ARTERIAL PRESSURE (HAMILTON) TO THE VALSALVA MANEUVER IN PATIENT C. B., FEMALE, AGED 49, BEFORE AND AFTER VERATRUM VIRIDE

Despite a marked reduction of the basal arterial pressure the overshoot response after the Valsalva was not blocked by veratrum.

first fell and then returned approximately to control values in five patients (Table IV) while in one patient (B. H., Table IV), who had marked impairment of renal function and low clearances in the control period, the inulin clearance fell and remained below the control values.

In contrast to the relatively moderate fluctuations in effective renal plasma flow, in glomerular filtration rate (inulin) and in filtration fraction, the urine volume was invariably and often strikingly reduced after the parenteral injection of veratrum viride (Table IV, Figure 4). The oliguria was associated with a marked increase in the U/P ratio of inulin or mannitol, clearly indicating that the diminished urine flow was due to increased tubular reabsorption of water. The marked rise in U/P ratio of para-aminohippurate was shown in one case (E. S., Table IV, Figure 4) to be due to increased water reabsorption exclusively since in this case the renal extraction of PAH as measured directly in the renal venous blood did not change despite marked oliguria and more than tenfold increase in urine concentration of PAH.

Oliguria occurred after parenteral injections of Veratrone even when there was no perceptible reduction in blood pressure. This was demon-

TABLE V

Vasopressor responses to the valsalva maneuver before and after the administration of veratrum viride

Patient	Control			After veratrum		
	Arterial pressure		Overshoot*	Arterial pressure		Overshoot
	Basal	After valsalva		Basal	After valsalva	
	mm. Hg	*mm. Hg*	*per cent*	*mm. Hg*	*mm. Hg*	*per cent*
I. B.	282/182	308/188	7	228/156	256/180	14
M. S.	240/130	290/178	26	194/102	263/132	33
M. A.	222/123	261/142	17	110/60	124/62	9
J. Mc.	270/160	290/180	9	170/105	178/111	6
J. F.	257/110	290/110	9	180/88	168/81	0
C. B.	238/158	272/170	11	120/76	160/108	37

* Calculated from the "mean" (one-half the sum of systolic and diastolic) pressure.

TABLE VI

The vasopressor responses to the quick tiltback from the upright to the horizontal position before and after the administration of veratrum viride

Patient	Control				After veratrum			
	Arterial pressure			Overshoot*	Arterial pressure			Overshoot
	Basal	After standing 5 min.	Tiltback overshoot		Basal	After standing 5 min.	Tiltback overshoot	
	mm. Hg	*mm. Hg*	*mm. Hg*	*per cent*	*mm. Hg*	*mm. Hg*	*mm. Hg*	*per cent*
C. B.	273/170	274/180	295/182	8	118/80	98/76	130/85	9
M. A.	221/132	193/129	260/148	16	112/69	99/76	155/80	30
J. Mc.	277/172	277/187	268/174	0	158/88	120/94	154/90	0
J. F.	260/112	262/117	280/115	6	194/89	176/94	202/90	3

* Calculated from the "mean" (one-half the sum of systolic and diastolic) pressure.

strated in two normotensive subjects in whom 5 per cent glucose in water was administered intravenously at a constant rate until a steady state of urine excretion was obtained as determined by washing out the bladder at ten-minute intervals. A dose of 0.4 cc. of Veratrone caused no significant change in blood pressure, but did reduce the urine volume from 5.45 and 8.33 cc. per minute to 1.02 and 4.53 cc. per minute, respectively, in the two patients. Oliguria was not observed when the reduction in blood pressure was maintained by the continued oral administration of veratrum viride (patients W. G. and A. D., Table IV).

IV. *Other hemodynamic functions*

Cardiovascular reflexes—Sympathetic responses

Unlike sympatholytic agents, veratrum viride did not abolish reflex sympathetic vasoconstriction. In six hypertensive subjects the vasopressor overshoot following the Valsalva maneuver was increased in three cases, slightly decreased in two, and abolished in one after as compared with before veratrum viride (Table V, Figure 5). Postural hypotension was not observed in four subjects who were tilted to an angle of 75° for five minutes (Table VI). The hypertensive overshoot on the tilt back from the erect to the supine position was increased in two of these cases, decreased in one and not present in one case (Table VI). Postural hypotension occurred in only two of 54 patients treated clinically with veratrum viride by mouth (5). Postural hypotension with collapse never occurred with therapeutic doses of the drug.

In contrast with the depression of the cold pressor response after certain sympatholytic agents (19–21) there was an augmentation after veratrum viride in two of four subjects examined and no change in the other two (Table VII). Similarly, the hypertensive response evoked in a subject by the emotional stimulus of a problem in mental arithmetic was not significantly altered during veratrum hypotension.

Reflex vasoconstriction in the digits was examined in two patients before and after the injection of veratrum viride. Finger plethysmographic recordings of the vasoconstrictor responses to a deep breath, the application of ice to the forehead and pin prick on the skin were if anything increased after veratrum viride. Further, in four patients examined in a room maintained at a constant temperature of 68° F there was no change in the skin temperature of the digits after the administration of Veratrone despite the development of marked

TABLE VII

Responses to the cold pressor test before and after the administration of veratrum viride

Patient	Control			After veratrum		
	Arterial pressure		Increase*	Arterial pressure		Increase
	Basal	Peak response to ice		Basal	Response to ice	
	mm. Hg	*mm. Hg*	*per cent*	*mm. Hg*	*mm. Hg*	*per cent*
J. F.	287/113	297/118	4	191/88	238/108	24
J. Mc.	282/168	325/194	15	167/100	228/136	36
M. S.	230/145	270/180	20	145/95	180/110	21
P. P.	238/145	300/200	30	143/95	210/134	44

* Calculated from the "mean" (one-half the sum of systolic and diastolic) pressure.

TABLE VIII

Effect of veratrone on blood flow in sympathectomized extremities

Case no.	Patient and diagnosis	Sex	Age	Drug and dose	Control			After veratrone			
					Arterial pressure	Blood flow per 100 cc. limb volume		Time after drug	Arterial pressure	Blood flow per 100 cc. limb volume	
						Lt. arm	Lt. leg*			Lt. arm	Lt. leg*
					m. Hg	*cc.*	*cc.*	*minutes*	*mm. Hg*	*cc.*	*cc.*
1	M. Q. Essential hypertension lumbodorsal splanchnicectomy through L2 lower extremities sympathectomized	F	35	Veratrone 0.5 cc.	209/136	1.45	1.76	6 18 22 31 43 67 89 101	205/149 185/125 158/114 142/106 122/92 144/110 171/117 170/125	1.78 1.96 2.31 2.10 1.79 1.63 1.96 1.90	— — — — 1.11 1.13 1.13 1.13
						Rt.* arm	Lt. arm			Rt.* arm	Lt. arm
2	L. O'S. Essential hypertension right transthoracic sympathectomy	F	24	Veratrone 0.5 cc.	227/145 230/148 229/156	1.70 1.68 1.64	1.43 1.49 1.58	3 24 41 59	253/159 213/134 181/123 175/123	2.03 1.50 1.37 1.33	1.65 1.78 1.82 1.78
						Rt.* leg	Lt. leg			Rt.* leg	Lt. leg
3	E. R. Essential hypertension right lumbar sympathectomy right lower extremity sympathectomized	F	40	Veratrone 0.7 cc.	175/100 177/103	1.68 1.78	1.16 1.07	8 23 38 43 65 86	179/105 146/93 129/81 129/83 134/84 146/89	1.77 1.80 1.90 1.71 1.69 1.88	1.42 1.42 1.50 1.35 1.32 1.20

* Sympathectomized.

reductions in blood pressure. These various observations show that the drug did not block sympathetic reflexes.

However, evidence that the sympathetic nervous system may be involved in some way in the depressor response was suggested by the data regarding blood flow through sympathectomized extremities. The effect of Veratrone on the blood flow in sympathectomized as contrasted with normally innervated extremities was studied in five patients. Three, who were hypertensives, manifested a significant hypotensive response to the drug (Table VIII). Two of them showed a persistent decrease in blood flow in the sympathectomized extremity, whereas the flow in the normally innervated control limb was increased. In the third patient there was a slight increase in blood flow in both extremities, greater in the normally innervated limb, but the results may have been affected by the presence of considerable pain. In the two normotensive subjects similarly studied after veratrum viride there were insignificant changes in both blood flow and arterial pressure.

Reaction to ephedrine and epinephrine

Veratrum did not abolish the pressor response and rise in heart rate following the injection of either epinephrine or ephedrine. The intramuscular injection of 0.05 gm. ephedrine promptly abolished the collapse reaction observed in three patients who were given an overdose of veratrum viride.

Vascular distensibility in the extremities

The vascular distension that occurs during venous congestion of the extremities (18) was measured in the forearm and calf in eight hypertensive and three normotensive patients before and after the intramuscular injection of Veratrone. The distension of the forearm segment in the plethysmograph during inflation of a congesting cuff to 30 mm. Hg was definitely greater after

Veratrone than before in five of 11 patients. In four the vascular distensibility was only slightly greater and in two there was no change. In the calf of one of six subjects studied there was a marked increase in vascular distensibility, in three a slight increase, and in two no change. No qualitative differences were observed between the normotensive and hypertensive cases.

Vascular distensibility measured in the sympathectomized lower extremities of two patients did not increase after Veratrone whereas in the normally innervated upper extremities it showed a marked increase. In the sympathectomized forearm of one patient there was a minimal increase in vascular distensibility after Veratrone while in the contralateral normally innervated forearm there was a marked increase.

These changes in the vascular distensibility after Veratrone occurred early and persisted for the duration of the experiments. They were usually greater and occurred earlier in the forearm than in the calf. There was little correlation between these changes and the alterations in blood pressure, blood flow, or calculated peripheral resistance.

Systemic response to venous congestion of the extremities

Previous observations in this laboratory have demonstrated that sodium nitrite and various sympatholytic agents alter markedly the systemic response of normal and hypertensive subjects to venous congestion of the extremities (22). In this test, the legs and one arm of the supine subjects were congested by cuffs placed proximally and inflated to pressures of 100 mm. Hg. After a hypotensive dose of sodium nitrite or of various sympatholytic drugs, patients frequently developed marked hypotension and collapse within two to five minutes following the application of the congesting pressure. By contrast, despite marked reductions in the resting blood pressure after veratrum, the application of such congesting pressures to the extremities for a period of five minutes was well tolerated in five subjects.

DISCUSSION

The hypotensive response to veratrum viride occurred in two phases: (*1*) an initial adjustment phase followed by (*2*) a more stable hypotensive phase. The first phase was characterized by sharp, and often fluctuating, decreases in arterial pressure, pulse rate and peripheral blood flow. The second phase consisted of a steady state of reduced arterial pressure and pulse rate, with a return of hepatic, renal and muscle blood flows to control values. Cardiac output in the second phase was found to be essentially unchanged from the pretreatment control values. These findings along with the decreased arterial pressure were accepted as indicating a decrease in peripheral resistance.

The decrease in peripheral resistance after veratrum viride appeared to occur in all the areas under study including the retinal arterioles (5, 23). Compensatory tachycardia and palpitation of the type produced by the peripherally-acting vasodilators such as sodium nitrite or tetraethylammonium salts did not appear, nor did postural collapse occur with sub-toxic doses of the drug. Vasopressor responses to the Valsalva experiment, the erect posture, the cold pressor test and emotional stimuli remained intact. Thus, a state of circulatory equilibrium was achieved with normal cardiac output and blood flow to the vital organs in spite of the lower arterial pressure. This integrated type of hypotensive response after the crude drug was similar to that observed in experimental animals after the administration of the pure alkaloids of veratrum (2), suggesting that it too was mediated through nervous reflexes involving the higher vasomotor centers.

While the second, stable phase of the hypotensive reaction to veratrum viride was characterized by generalized vasodilatation and a return of blood flow to normal, the initial falling phase of the reaction appeared to involve different mechanisms since it not infrequently was associated with parallel decreases in peripheral blood flow. Therefore, the initial fall in arterial pressure could not always be due to a generalized decrease in peripheral resistance. A depression of cardiac output might well account for the initial fall in arterial pressure. It need not be primary in the heart but could result from a temporary failure of venous return due to dilatation of the post-arteriolar vascular beds and a consequent relative shift of circulating blood volume from the arteries to the capillaries and veins. Neither need a depression in cardiac output be sizable to cause a marked fall in arterial pressure provided it continue for some minutes. It is

known that large decreases in cardiac output such as occur with the Valsalva experiment are capable of lowering the arterial pressure of hypertensive patients to normal within a few seconds (15). An immeasurable decrease in cardiac output therefore might cause a similar effect if continued over a longer period of time such as that required for the arterial pressure to stabilize at a lower level after veratrum. Studies now in progress (24) on the changes in cardiac output during the initial phase of the hypotensive action of veratrum may reveal decreases of cardiac output to occur, but in the light of the above argument, they may not.

The oliguria which followed the parenteral injection of veratrum viride appeared to be independent of changes in either glomerular filtration rate or renal plasma flow, since suppression of urine volume continued to be most marked when these measurements had returned to or above control values. The oliguria seemed to be independent also of the level of arterial pressure inasmuch as it was observed to occur following parenteral doses of veratrum insufficient to cause a significant reduction of blood pressure, and to disappear when a continuous hypotension was maintained by prolonged oral administration of the drug. The lack of direct mechanical dependence upon either arterial pressure, glomerular filtration rate or renal plasma flow indicated that the oliguria was due to a specific antidiuretic effect. This conclusion was further substantiated by the regular occurrence of a marked rise in the U/P ratio of inulin or mannitol during the period of depressed urine volume indicating an increased tubular reabsorption of water. In addition, the extraction of PAH from the blood, as measured directly in the renal vein, did not change appreciably during the period of oliguria. These data were interpreted as indicating that the kidneys usually cleared the blood as efficiently after veratrum as they had prior to the induced hypotension but did so at first with the production of a small volume of highly concentrated urine. Therefore, the oliguria induced by the acute administration of veratrum viride did not indicate severe impairment of renal function as has been postulated previously (25), but rather a transient antidiuresis, which disappeared with continued oral treatment.

Whereas mannitol clearances fell and remained low after veratrum viride, inulin clearances fell initially but usually returned to control values despite a continued reduction in arterial pressure. This discrepancy between the clearances of mannitol and inulin was not surprising in view of the recent evidence that under certain circumstances mannitol may be partially reabsorbed in the tubules (26). The increased tubular reabsorption of water which followed the parenteral injection of veratrum viride might well tend to accelerate the back-diffusion of mannitol, and thereby, to aggravate the discrepancy between the clearances of mannitol and inulin.

Since reflex vasopressor responses and also the vasoconstrictor reactions in the hands and feet all remained intact after veratrum viride, the drug did not appear to block sympathetic vasoconstriction. However, it is interesting that with the fall in blood pressure there was a decrease in blood flow in the sympathectomized extremities of two patients, as contrasted with the increase that occurred in the normally innervated control limbs. The decrease in the sympathectomized limbs may have been the passive result of the reduction in arterial pressure and the increase in the control limbs the result of active sympathetic vasodilatation. In this connection it was of interest also that after veratrum there was an increase in vascular distensibility in normally innervated limbs as contrasted with little or no change in sympathectomized limbs. Thus, while there was no evidence that sympathetic vasoconstrictor reflexes were blocked there was indication that vasodilator responses mediated over the sympathetic nerves might be stimulated. Finally, atropine abolished the bradycardia but did not reverse the hypotensive effect suggesting that the fall in arterial pressure was not dependent upon parasympathetic stimulation.

As a result of these studies one might draw the clinical implication that veratrum viride should be a suitable therapeutic agent in essential hypertension since it can reduce the blood pressure without harmful effects on the heart or kidneys (except when the function of the latter is severely impaired) and, since it leaves intact the vasomotor reflexes, particularly those concerned with assuming the erect posture. However, during actual clinical trial it has caused frequent toxic side reactions, the most prominent of which are nausea and vomiting (5). Work so far indicates that

these reactions may be an integral part of the reflex pattern activated by the drug (2). Therefore, the possibility of isolating or developing a compound of veratrum that will retain the desirable cardiovascular effects of the crude drug and eliminate the toxic side effects does not at present appear to be very promising.

SUMMARY AND CONCLUSIONS

Veratrum viride administered to hypertensive patients produces the following hemodynamic effects:

1. Blood flow through muscular, renal, and hepatic-portal areas usually falls initially and then returns to approximate control levels despite a continued hypotensive response. Full peripheral vasodilatation characteristically follows rather than accompanies the initial reduction in arterial pressure.

2. The output of the compensated heart remains essentially unchanged after arterial pressure is reduced. In congestive heart failure cardiac output may increase and the elevated pulmonary arterial pressure may fall.

3. Atropine abolishes the bradycardia induced by veratrum viride but only partially reverses the hypotension. Since the hypotensive effects do not depend necessarily upon a reduction in either cardiac rate or output, there is little evidence to indicate that the drug is a "cardiac depressant."

4. Effective renal plasma flow decreases only transiently and returns to control values despite a continued reduction in arterial pressure after veratrum. Glomerular filtration rate (inulin) follows a similar pattern in most cases, but occasionally remains below control values.

5. Oliguria occurs after the initial injection of veratrum viride but disappears when the hypotensive effect is continued by repeated oral administration of the drug. The oliguria is not related directly to the arterial pressure, glomerular filtration rate or renal plasma flow, but appears to be due to a specific antidiuretic effect.

6. The discrepancy between inulin and mannitol clearances is confirmed, the mannitol clearances usually remaining lower than those obtained with inulin. This discrepancy seemed to be accentuated during marked antidiuresis suggesting increased tubular reabsorption of mannitol.

7. Veratrum viride does not inhibit sympathetic vasoconstrictor responses as evidenced by the maintenance of vasopressor overshoots, skin temperature levels, vascular reflexes in the digits, the cold pressor response, and postural adaptation.

8. Vascular distensibility in the extremities usually increases, except in sympathectomized limbs, but not necessarily in association with alterations in arterial pressure, blood flow or peripheral resistance.

9. During the period of reduced arterial pressure, blood flow and vascular distensibility in sympathectomized as compared with normally innervated extremities do not increase, indicating that part of the vascular response in the limbs may be mediated over sympathetic nervous pathways possibly through sympathetic vasodilator fibers.

10. Epinephrine and ephedrine reverse the hypotensive effects of veratrum.

11. The evidence cited indicates that veratrum can produce an integrated hypotensive response which is not associated with toxic effects on either the heart or the kidneys.

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