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COMPARATIVE STUDY OF THE EFFECTS OF TETRAETHYL-AMMONIUM CHLORIDE AND VERATRUM VIRIDE ON BLOOD PRESSURE IN NORMAL AND TOXEMIC PREGNANCY

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Persistence of elevated blood pressure in toxemia of pregnancy following autonomic blockade with tetraethylammonium chloride (TEAC) has been reported previously by the authors (1). Subsequently many of the patients studied were treated with subcutaneous veratrum viride with consistent depressor effects. The apparent opposing actions of these two drugs in toxemia, together with a suggestion that one tends to negate the effect of the other, have served as the stimulus for the present study.

In an effort to obtain suggestions as to the site and mechanism of action of veratrum, it was decided to compare blood pressure responses to both veratrum and TEAC intravenously in the same patients. The latter drug, an autonomic blocking agent, has been demonstrated to produce diametrically opposite blood pressure effects in normal pregnancy and toxemia (1). In toxemic pregnancies, TEAC invoked negligible blood pressure responses with persistence of diastolic hypertension, whereas in normal pregnancies the same drug invariably produced a fall in the diastolic blood pressure to levels of 50–60 mm. Hg. These results were interpreted as indicating a predominance of humoral tone in toxemic hypertension as opposed to a predominance of neurogenic tone in normal pregnancy at term.

Thus, this comparative study of blood pressure responses of toxemic and normal pregnant patients was undertaken in an effort to quantitate the depressor effect of veratrum, to seek clues as to its pharmacologic action, and to correlate further the humoral and neurogenic interrelationships postulated by previous studies.

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MATERIAL AND METHODS

Ten normal pregnant patients and 12 patients with toxemia of pregnancy were studied. In the toxemic group, two patients had convulsive eclampsia and ten were designated as severe preeclampsia. Diagnostic criteria were the same as utilized in the previous study (1). Six primiparae and four multiparae comprised the normal pregnant group. Toxemias included six primiparae and six multiparae. The length of gestation was approximately the same in both groups.

Blood pressure responses were recorded both prepartum and following delivery. Normal pregnant patients were tested at term, prior to the onset of labor, and again within 36–60 hours postpartum. In the preeclamptic group prepartum assay was conducted at the height of clinical toxemias and again following postpartum recovery (in two cases the postpartum response was recorded coincident with obvious clinical improvement, yet persistence of albuminuria indicated that the disorder had not completely abated). Therapy was withheld prior to all prepartum tests and discontinued at least 24 hours before postpartum assay.

Assay was performed in the following manner. After stabilization of the blood pressure in the supine position, 4 cc. (400 mgm.) of TEAC were injected intravenously. Sphygmomanometer readings taken at half-minute intervals indicated the lowest level to which the blood pressure fell in the first five minutes following the injection, *i.e.*, the *TEAC floor*. Pulse rates were counted at the radial artery.

After the effects of TEAC had disappeared (usually within two hours), 0.2 cc. (3 minims) of veratrum viride² were then injected intravenously.³ Half-minute sphyg-

² Veratrone, the veratrum preparation utilized in this study, was supplied by Parke, Davis & Co. through the courtesy of Dr. E. C. Vonderheide. In order to minimize possible error due to variations in stability and standardization, all Veratrone used was supplied by the manufacturer from the same factory lot at the time of preparation.

³ Previous to this study, the intravenous technique was standardized for toxemic patients in the following manner: The drug was first administered intravenously by tuberculin syringe in consecutive 0.065 cc. (1 minim) doses at in-

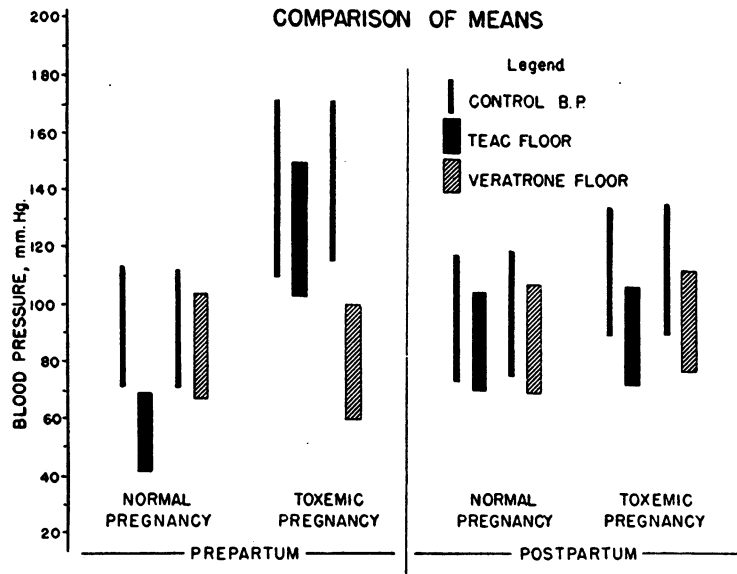


FIG. 1. THE MEAN TEAC AND VERATRUM BLOOD PRESSURE FLOORS FOR TEN NORMAL AND 12 TOXEMIC PATIENTS IN BOTH PREPARTUM AND POSTPARTUM PERIODS

Note the height of the toxemic TEAC floor prepartum in contrast to the low floor following veratrum in the same patients.

momanometer readings were taken for eight to ten minutes and thereafter at one-minute intervals for 20 minutes. The lowest point to which the blood pressure descended in the first 10 minutes following the injection has been termed the *veratrum floor*. The pulse rate was carefully followed.

In an effort to evaluate possible antagonistic blood pressure actions of TEAC and veratrum, a second injection of 4 cc. of TEAC was given to six of the normal pregnant patients and to six of the toxemics at the seventh to tenth minute following veratrum, *i.e.*, at the height of the depressor action. In these patients, blood pressure and pulse recordings were continued for an additional 15 minutes following the second injection of TEAC.

RESULTS

The blood pressure responses to TEAC and veratrum in normal pregnancy and toxemia offer striking contrast. Whereas the toxemic TEAC

intervals of several minutes. Blood pressure responses of ten toxemic patients were assayed in this manner with total dosage ranging from 0.2 to 0.6 cc. of the drug. These studies led to the adoption of 0.2 cc. as a standard intravenous dose, because this amount of veratrum reduced the blood pressure to a normal range in all the patients surveyed. The greatest blood pressure fall to the dose employed occurred from seven to ten minutes following injection and lasted for 45 to 70 minutes. The details of the intravenous technique are reported elsewhere (2).

floor is persistently elevated, veratrum (in the dose employed) consistently causes a lowering of the toxemic blood pressure to hypotensive levels. The same amount of veratrum invokes only negligible responses in normal term pregnancy, yet TEAC invariably produces marked depressor effects in this group.

Normal term pregnancy: The results are shown in Figure 1 and Table I. Prepartum TEAC floors ranged from 50/30 to 88/64 with a mean of 69/42 mm. Hg. The mean control blood pressure was 113/72 mm. Hg. The minor magnitude of the veratrum response is reflected by the mean prepartum veratrum blood pressure floor of 103/67 mm. Hg from a mean control blood pressure of 111/71 mm. Hg. Following delivery the TEAC floors rose promptly to normal while veratrum floors remained essentially unchanged.

Although veratrum produced only negligible blood pressure effects in this group, its administration was attended by bradycardia and nausea in most instances (the heart rate increased in two patients). Vomiting occurred in approximately 40% of the tests. Oral and epigastric burning (within one-half minute after injection), sensations of excessive warmth, and profuse diaphoresis

were noted regularly. Extreme apprehension attended the appearance of these manifestations.

Toxemia: TEAC invoked only slight to moderate depressor effect in the presence of toxemia prior to delivery. From a mean control level of 171/110 mm. Hg the mean TEAC floor was 150/103 mm. Hg. This was in marked contrast to a mean prepartum veratrum floor of 100/60 mm. Hg, though control levels were approximately the same (Figure 1, Table I). With postpartum clearing of toxemia the mean TEAC floor of 106/72 mm. Hg was very similar to that of veratrum, 112/77 mm. Hg.

The concomitant effects of veratrum again were prominent. Bradycardia was observed 17 times in 24 tests. The blood pressure fell, however, regardless of whether or not the heart rate slowed. Vomiting occurred in one-half the tests; oral and epigastric burning, nausea, sweating, warmth and apprehension were universal complaints.

Comparison of depressor responses: The blood pressure responses to the two drugs are compared

in Figure 2. Results have been plotted in percentages to depict the magnitude of the depressor responses, in terms of effect on the total blood pressure. It should be noted that veratrum caused a 42% systolic and a 48% diastolic lowering of the toxemic blood pressure in the dose employed, whereas the same dose in normal term pregnancy produced only negligible response (6% systolic; 5% diastolic).

Conversely, autonomic block with TEAC exerted its greatest lowering effect in normal pregnancy (38% systolic, 41% diastolic), and invoked only minimal response in toxemia (12% systolic, 6% diastolic).

Response to TEAC administered at height of veratrum action: The injection of TEAC consistently dispelled the concomitant effects of veratrum, but blood pressure responses showed considerable variability. Bradycardia, epigastric burning, nausea, vomiting, and sweating ceased immediately following injection, and a feeling of well-being replaced the previous apprehension.

TABLE I
Blood pressure effects of TEAC (4 cc.) and veratrum viride (0.2 cc.), administered intravenously in normal and toxemic pregnancy during prepartum and postpartum periods

NORMAL TERM PREGNANCY	PREPARTUM				POSTPARTUM			
	Control B.P.	TEAC Floor	Control B.P.	Veratrone Floor	Control B.P.	TEAC Floor	Control B.P.	Veratrone Floor
1. B.P.	105/61	64/40	110/66	104/64	108/75	102/74	117/78	110/76
2. B.W.	102/69	50/30	101/69	100/68	112/69	92/62	116/70	104/68
3. P.W.	119/79	76/42	123/81	108/70	118/79	100/70	116/78	104/68
4. L.L.	119/70	68/44	120/71	118/68	122/80	110/76	121/81	110/68
5. M.W.	115/79	88/64	114/72	100/70	120/72	108/64	119/70	110/68
6. M.Sa.	117/80	68/44	107/72	105/70	114/68	110/74	118/78	112/78
7. B.S.	116/80	75/48	110/79	104/70	124/85	110/78	120/81	100/78
8. E.S.	121/70	68/40	121/71	112/68	121/72	118/68	122/72	108/64
9. T.C.	104/60	66/30	101/59	90/60	128/70	100/70	128/71	110/58
10. E.H.	109/69	70/40	104/69	95/65	101/60	80/60	104/68	98/68
TOXEMIA OF PREGNANCY								
1. A.D.	212/127	180/120	191/121	120/80	167/111	112/70	182/125	140/100
2. G.R.	165/118	135/98	161/120	90/50	149/98	104/60	143/96	110/60
3. F.M.	175/103	165/105	193/114	100/60	114/81	70/50	120/92	88/70
4. L.H.	153/100	130/90	151/108	105/45	114/74	102/68	118/75	114/68
5. M.Wa.	171/110	195/130	204/131	130/85	119/74	100/68	121/76	96/70
6. V.W.	160/109	130/100	142/109	90/50	119/86	106/74	110/79	100/66
7. M.F.	177/104	140/92	180/119	100/60	168/101	124/80	179/108	130/80
8. L.R.	177/111	150/110	182/112	125/82	131/92	100/75	130/92	120/90
9. M.Sm.	155/100	130/90	180/110	120/58	131/82	110/70	127/81	114/76
10. R.H.	170/110	150/100	162/108	85/60	124/82	110/80	130/81	100/70
11. R.B.	180/120	145/100	172/119	80/50	145/98	120/90	142/94	118/88
12. E.T.	151/110	145/100	152/110	60/40	134/90	120/84	132/88	120/82

Blood pressure in mm. Hg

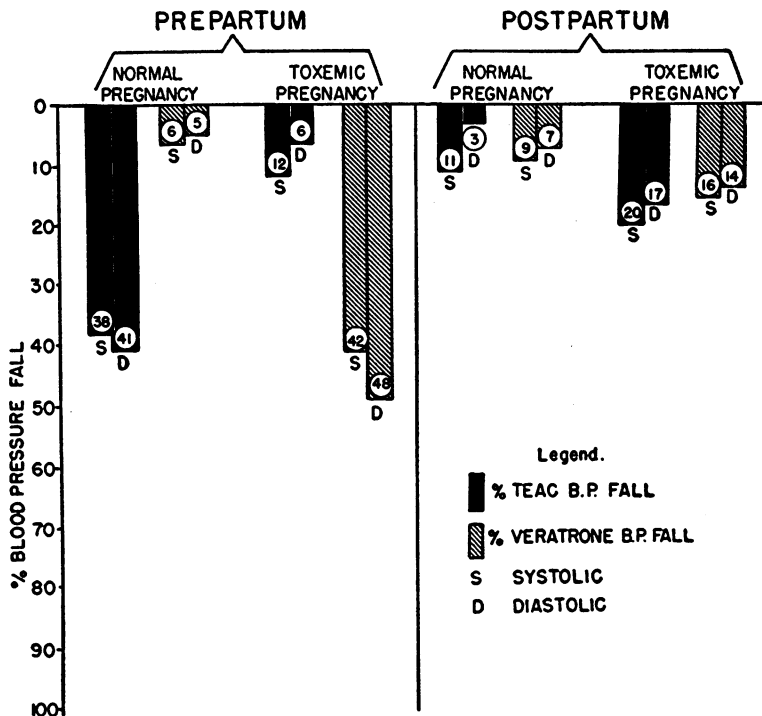


FIG. 2. THE BLOOD PRESSURE RESPONSES TO TEAC AND VERATRUM OF NORMAL AND TOXEMIC PATIENTS, EXPRESSED AS PERCENTAGE FALL FROM CONTROL LEVELS

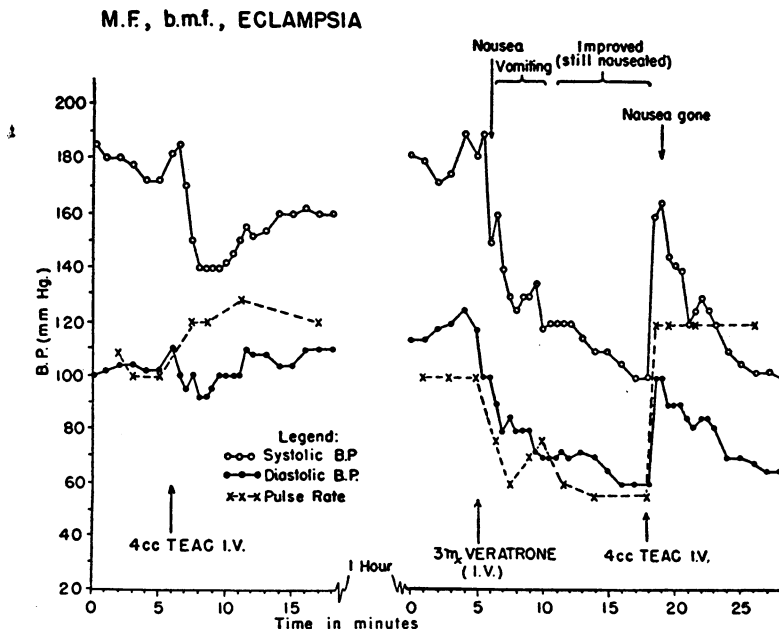


FIG. 3. COMPARISON OF THE BLOOD PRESSURE EFFECTS OF TEAC AND VERATRUM VIRIDE AND OF TEAC DURING VERATRUM ACTION IN A CASE OF ECLAMPSIA

In general, if the blood pressure had been markedly depressed by veratrum, TEAC invoked a temporary pressor response of varying magnitude and duration. As this response to TEAC subsided, the blood pressure descended again to the range of the veratrum floor; however, bradycardia and the other side effects of the drug did not reappear. The pattern of response most frequently encountered in toxemia is shown in Figure 3. The low TEAC floors of normal term pregnancy were reproduced after veratrum, but the responses were of slightly less magnitude than before.

DISCUSSION

A satisfactory pharmacologic explanation of the vasodilator and vasodepressor effects of veratrum alkaloids is not yet available. Studies demonstrating that the action is not directly on the blood vessel walls have been reviewed by Krayer and Acheson (3). The vasodilatation has been stated to be reflex nature with the afferent pathways running mainly in the vagus nerves (4-6). The depressor responses following veratrum alkaloids have not been abolished by artificial respiration (5), vagal section (5, 7), or atropine (5, 8). These bits of evidence, recently supplemented by Freis' (9) demonstration that the drug does not significantly affect cardiac output in man, suggest that arteriolar resistance is diminished after veratrum viride administration.

Tetraethylammonium chloride, by producing a pharmacologic blockade of the autonomic ganglia, causes a reduction in arteriolar tone (10) and probably venous tone as well (1). Cardiac output is not relevantly affected (10).

In this study, no attempt was made to obtain maximal depressor responses with veratrum in toxemia. Instead, the smallest dose which effectively lowered blood pressure in a pilot group of toxemic patients was selected. It is quite striking that this small amount (0.2 cc.) invariably reduced the hypertension associated with toxemia, yet did not affect the blood pressure of the normal pregnant woman. This absence of depressor response to veratrum in normal pregnancy has been observed previously by Assali and his associates (11) after subcutaneous doses ranging up to 0.78 cc. Whether larger doses would produce depressor effects in normal pregnant women cannot be stated from this study. Also noteworthy is the

fact that the prominent veratrum depressor responses in the toxemic group disappeared promptly following delivery and recovery from toxemia. These findings indicate an unusual and consistent responsiveness of toxemic hypertension to veratrum in the dose employed.

The opposing actions of TEAC and veratrum in both normal pregnancy and toxemia allow for interesting speculation as to the reasons for this apparent pharmacologic antagonism. Persistence of toxemic hypertension following TEAC has been interpreted to indicate activity of humoral mechanisms in sustaining hypertension in these patients (1, 12). Since veratrum invariably lowers the blood pressure in toxemia, it might be inferred that this drug acts specifically on or against the supposed humoral control of toxemic hypertension. At the present, however, there is insufficient evidence to substantiate such an inference.

Available evidence to date suggests that the most likely explanation for the vasodepressor action of veratrum is stimulation of vasodilator fibers of the autonomic nervous system. This mechanism which has been suggested by others (9) could explain many of the blood pressure phenomena observed in this study. The transient pressor response to TEAC which occurs during the depressor action of veratrum in toxemia might well be explained by a blocking effect of TEAC on vasodilator impulses. Although sympathetic vasodilator fibers have been demonstrated by many investigators (13-15), evidence that veratrum reduces blood pressure by producing active vasodilatation through stimulation of this system is still lacking.

The effect of TEAC (first injection) on the patients in this study followed the same pattern as previously reported (1), *i.e.*, marked fall in blood pressure in normal pregnancy, negligible response in toxemia and reversion of blood pressure floors of both groups to normal levels following delivery and recovery.

The excessive fall in blood pressure obtained after TEAC in *normal* pregnancy has been attributed in part to exaggeration of venous pooling in the lower extremities where the venous pressure is already elevated. A release of neurogenic venous tone following TEAC was thus postulated. Observations during caudal anesthesia by Masters (16), and spinal anesthesia by Roman and Adriani

(17) offer additional support for this concept. The latter authors have also observed an abrupt rise in the blood pressure of normal pregnant patients subjected to Caesarean section under spinal anesthesia, following emptying of the uterus. This correlates closely with the rise in the postpartum TEAC floor observed in normal pregnancies. Furthermore, it suggests that the increased abdominal pressure and heavy uterus, by compressing the inferior vena cava and iliac veins, may be a major factor in increasing the venous pooling in the lower extremities, after autonomic blockade with either TEAC or spinal anesthesia.

Additional evidence for this is offered by the repeated observation (18) during the height of depressor action of TEAC in term pregnancy that the blood pressure consistently rose when the patient was turned to either side and fell again when the supine position was resumed.

Interestingly, although veratrum consistently abolished toxemic hypertension and frequently produced very low blood pressure levels, there was no suggestion that venous tone had been markedly diminished. Adaptation to posture was not affected. Freis' recent study of veratrum in essential hypertensives (19) also failed to produce evidence of postural hypotension following the drug. Thus, there are indications that while TEAC in blocking the autonomic ganglia releases both arteriolar and venous neurogenic tone, veratrum spares the veins in producing its vascular effects, which may account in part for the minor depressor action of veratrum in normal term pregnancy.

The frequency and regularity with which bradycardia, epigastric burning, nausea, and vomiting appeared following veratrum suggest that these should be regarded as concomitant effects of the drug, rather than as toxic manifestations resulting from overdosage. Usually these effects were noted whether or not the blood pressure was lowered, yet in several toxemic patients they were not prominent despite marked blood pressure reduction. In addition, they were promptly dispelled by TEAC in all instances, even though in the toxemias the depressor action continued. These effects can be accounted for by stimulation of parasympathetic pathways, and their abolition then would be expected when TEAC blocks the autonomic ganglia. Similar experiences have been reported by Moe and his associates (20) with

veratridine in studies on anesthetized dogs. They believe that TEAC prevents the reflex cardiovascular responses by interrupting ganglionic transmission in the efferent limb of the arc. These observations are of help in separating the depressor action of veratrum from its troublesome side effects. The magnitude of the depressor response was repeatedly noted to be independent of the severity of the side effects.

It was previously reported (1) that blood pressure assay with TEAC might offer some diagnostic assistance in toxemia of pregnancy. The opposing actions of TEAC and veratrum plus the consistent depressor effects of the standard dose of veratrum (0.2 cc.) in toxemia as opposed to negligible effects on the blood pressure in normal pregnancy allow for a further elaboration of blood pressure assay for diagnostic purposes in cases of borderline toxemia.

CONCLUSIONS

1. Blood pressure responses to intravenous TEAC and veratrum in normal term pregnancy and toxemia of pregnancy in prepartum and postpartum periods have been compared.
2. The blood pressure of the toxemic hypertensive consistently falls in response to veratrum in the dosage utilized in this study.
3. Diametrically opposing blood pressure effects of TEAC and veratrum have been demonstrated in both normal pregnancy and toxemia.
 - A. In normal pregnancy, prepartum, TEAC produces marked blood pressure fall, whereas veratrum invokes negligible responses.
 - B. In toxemia of pregnancy, TEAC causes only minimal blood pressure fall while veratrum invariably produces marked lowering of the blood pressure.
 - C. Bradycardia, nausea, and vomiting are encountered regularly following veratrum administration but are independent of the depressor action of the drug.
 - D. Administration of TEAC at the time of maximum veratrum effect immediately eliminates the concomitant manifestations of veratrum and in toxemia produces a transient pressor response.
4. Veratrum viride as employed in this study can be administered safely by the intravenous

route; its utilization in conjunction with TEAC blood pressure assay may offer diagnostic assistance in toxemia of pregnancy.

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