ADDITIVE ACTION OF TWO HYPOTENSIVE DRUGS IN PREGNANCY HYPERTENSION

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The ideal therapy for toxaemias of pregnancy should have the following basic approach:

(1) Correction of physiologic disturbance, viz., arteriolar spasm.
(2) Correction of metabolic disturbance, viz., retention of sodium and tissue fluid.
(3) Control of convulsions.
(4) Termination of pregnancy if above measures fail to bring about improvement.

In this clinical trial an attempt is made to deal with the first factor mentioned above, viz., arteriolar spasm.

Within the past few years, quite a few hypotensive drugs have been introduced. Therapeutically available effective agents are: (a) Veratrum alkaloids and (b) Rauwolfia Serpentina alkaloids.

Recently, the use of protoveratrine, the purified alkaloid of Veratrum Album has been reported by some workers. The intravenous administration of protoveratrine in hypertensive pregnant women seems to cause a rapid fall of blood pressure lasting for about 2 to 3 hours. The blood pressure fall is at times precipitate and is associated with severe vomiting and collapse. Its routine use in such circumstances, then, is limited because of its shorter duration of action and its frequent undesirable effects. Other group of workers have tried the effect of intravenously administered Reserpine in patients with pregnancy toxaemia. The fall of blood pressure has been relatively small after a latent period of about 2 hours, the action lasting for an average of 12 hours.

A desirable preparation would be one which produces a rapid and moderate fall of blood pressure for a prolonged period with no side effects. A parenteral preparation containing optimum proportion of protoveratrine and serpina alkaloids might serve the purpose. The present trial was conducted to evaluate such a preparation for the treatment of hypertension in pregnancy.

Paper read at the 10th All India Obstetric & Gynaecological Congress at Hyderabad in January 1959.

Material and Method

The drug preparation used for the present trial had the following composition:

Serpina alkaloids	..	5.0 mg./ml.
Reserpine	..	2.5 mg./ml.
Protoveratrine	..	0.15 mg./ml.

The usefulness of this compound was evaluated in 24 pregnant females with hypertension admitted to hospital. 17 cases were diagnosed as pre-eclampsia and 7 were of pregnancy with associated hypertension. The age varied from 18 to 39 years.

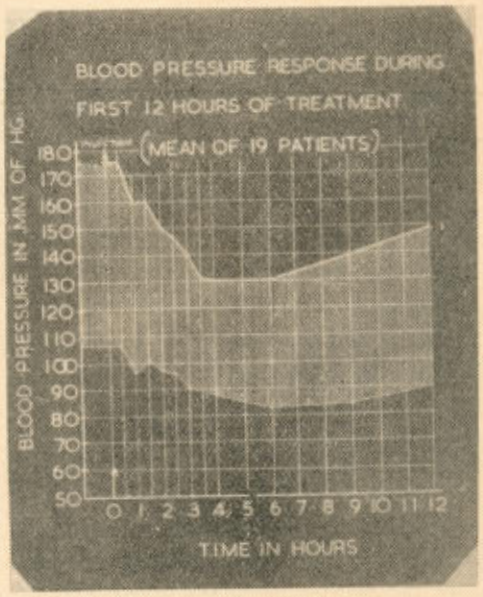
On admission of the patient, routine history, physical examination, retinoscopy and urine examination were carried out. Blood urea, N.P.N. and other special investigations were asked for when necessary. The patient was prescribed complete rest in bed and 'salt-poor' hospital diet. Intramuscular injection of 50% magnesium sulphate was advised when the patient was admitted with severe convulsions. This was only necessary in 2 patients. No other drug treatment or sedatives were given.

The initial amount of the drug administered was ½ ml. to 1 ml. intramuscularly, depending upon the severity of a case. Similar dose was repeated after about 4 hours if no desired fall of B.P. was obtained with previous injection. In patients with satisfactory pressure response, a maintenance dose of ½ to 1 ml. was injected when the blood pressure started rising. This was usually necessary after about 12-18 hours. The B.P. readings of all patients were recorded by one doctor in charge. The value noted was the lowest of two successive readings.

After the first injection, the blood pressure was taken every half an hour for first 4 hours, then every 3 hours for first 12 hours, and later on three times a day.

Results

Five patients with pre-eclampsia did not respond at all to the therapy. Rest of the 12 cases of pre-eclampsia and 7 of associated hypertension showed a satisfactory response. In favourable cases, following the first injection of the drug, the fall in systolic pressure varied from 5 mm. to 65 mm.Hg., and the fall in diastolic from 15 to 40 mm.Hg. The average fall of the systolic pressure was 35 mm.Hg. The average period for the onset of action of the drug was within one hour, and for the peak action about 4 hours. The effect lasted for about 12 hours. In a few instances, the effect lasted for more than 24 hours and in one case in fact the blood pressure fall was maintained for 5 days. For subsequent period, the blood pressure fall could be kept up by a maintenance dose of ½ to 1 ml. of the drug.



The clinical improvement of the patient's condition showed a linear relationship with the blood pressure

TABLE

Case no.	Age	Diagnosis	Initial B.P.	Average B.P. during treatment and before delivery	Duration of treatment
1	20	Pre-eclampsia	200/120	138/95	
2	32	Pre-eclampsia	175/110	145/85	17 hours
3	18	Pre-eclampsia	165/130	128/83	16 hours
4	30	Pre-eclampsia	165/115	135/95	
5	30	Pre-eclampsia	160/110	148/83	
6	20	Pre-eclampsia	180/100	144/75	20 hours
7	25	Pre-eclampsia	170/95	115/73	24 hours
8	30	Pre-eclampsia	210/130	200/125	60 hours
9	18	Pre-eclampsia	155/100	125/80	
10	20	Pre-eclampsia	155/105	145/95	20 hours
11	30	Pre-eclampsia	180/124	180/120	
12	30	Pre-eclampsia	200/110	169/97	
13	25	Pre-eclampsia	170/110	135/85	
14	22	Pre-eclampsia	160/100	125/75	32 hours
15	20	Pre-eclampsia	165/95	130/78	26 hours
16	25	Pre-eclampsia	142/95	135/75	10 hours
17	39	Pre-eclampsia	170/100	145/95	
18	23	Associated B.P.	170/120	140/86	17 days
19	20	Associated	140/100	115/75	
20	30	Associated	160/100	125/80	
21	28	Associated B.P.	175/100	135/75	
22	25	Associated	150/105	125/85	24 hours
23	20	Associated	155/100	135/76	
24	35	Associated	150/110	120/80	

response. However, this did not alter the fetal mortality rate. Side effects encountered with the present dosage formula were minimal. One patient felt transient giddiness and the second patient suffered from vomiting accompanying the sudden fall of B.P. The rest of the patients were free from any side effects except some local pain at the site of injection. When given in the deltoid region, the intramuscular injection was annoyingly painful. Hence it should be given deep in the gluteal region.

Comments

Prior to this series, we have tried, in another group of patients (not reported), two preparations, one containing 0.4 mg./ml. of protoveratrine and the other containing 0.25 mg./ml. of protoveratrine. Both the preparations were incorporated in a mixture of serpina alkaloids and reserpine in the same proportion as the present compound under trial. Both these previous preparations were effective in lowering the blood pressure, but unfortunately the frequent toxic effects precluded their further trial. The concentration of Protoveratrine was reduced to 0.15 mg./ml. in the compound. This new compound was tried in the present series. The toxic effects were minimum with this. The incorporation of

serpina alkaloids and reserpine in the compound appears to have additive, if not synergistic, antihypertensive action. They are also responsible for the longer duration of hypotensive effect.

Summary

A combination of serpina alkaloids and protoveratrine was given by intramuscular injection to 24 pregnant females with hypertension admitted to hospital. 17 cases were diagnosed as pre-eclampsia and 7 were of pregnancy with associated hypertension—24 total. 19 of them showed satisfactory response. The average dose was ½ to 1 ml. depending on the severity of the case. The B.P. fell on an average 32 mm.Hg. systolic and 22 mm.Hg. diastolic within an hour and the effect lasted for 12 hours. From our experience in the present series, it appears that the above combination of hypotensive drugs could prove effective in the management of pregnancy hypertensive toxaemia.

Conclusions

The result in this series shows that the fall of blood pressure is fairly quick and prolonged after a single intramuscular injection of the drug. The action starts within an hour, is maximum in four hours' time and lasts for an average of 12 hours. There is a moderate fall in both the systolic and diastolic pressure, the average systolic fall being 32 mm. Hg. and the average diastolic being 22 mm.Hg. From our experience in the present series, it appears that the above combination of antihypertensive drugs could prove effective in the management of hypertension of pregnancy. Its use can also be indicated in acute hypertensive states such as hypertensive encephalopathy and acute left ventricular failure associated with severe hypertension.

The various combinations of the alkaloids were kindly supplied by Unichem Laboratories. The present combination is called by the proprietory name of "Vera-tenshun."