HYPERTENSION IN PREGNANCY*

J. M. SAMSON, M.B., B.CH., DIP. O & G. (RAND), F.C.O.G. (S.A.), M.R.C.O.G., *Obstetrician and Superintendent, Bridgman Memorial Hospital, Johannesburg*

Hypertension in pregnancy has always been a problem, and pre-eclampsia has constituted its greatest challenge. Intensive research has failed to demonstrate the cause of pre-eclampsia, although the characteristic rise in blood pressure seems dependent upon arteriolar constriction. If this is so, treatment that relieves this arteriolar constriction should have a beneficial effect in pre-eclampsia and, possibly, other causes of hypertension in pregnancy. The purpose of this paper is not to enter into a discussion on the aetiological factors, but to present to you our experience with the use of a vasodilating hypotensive agent, viz. protoveratrine (puroverine-Sandoz).

In view of favourable reports by other authors[1-5] we have used this drug in the treatment of 120 Bantu patients admitted to the Bridgman Memorial Hospital, Johannesburg, with hypertension in pregnancy. Two forms of protoveratrine were used, both given orally in tablet form, viz.

1. Puroverine (PVS 295), the short-acting form, consisting of pure crystalized alkaloids of *Veratrum album* in the ratio 2/3rds of protoveratrine A to 1/3rd of protoveratrine B, each tablet containing 0·25 mg. of the total active substance. (The B fraction is known to be only 1/20th as effective as the A fraction and, consequently, it is not considered to contribute greatly to the clinical response.)

2. 'PVA retard', containing only the protoveratrine A fraction in a long-acting form. (The amount of total active substance is 0·3 mg., of which 0·1 mg. is released immediately, 0·1 mg. 3–4 hours later, and the remaining 0·1 mg. after a further 3–4 hours. Thus prolonged action is obtained without repeated dosage and patients are allowed undisturbed rest at night.)

Further routine treatment consisted of bed rest and salt-free diet, sedation being given only in very severe pre-eclampsia in the initial hours after admission. While treatment continued, the blood pressure was recorded every 2 hours during pregnancy, more frequently during labour, and daily throughout the puerperium. On discharge the blood pressure was again recorded and the final check made at the postnatal clinic.

Labour was not induced, medically or surgically, but was allowed to commence spontaneously, being terminated by forceps or Caesarean section only where other obstetrical indications were present.

Retrograde analysis of the presenting features in the patients in this series resulted in our distinguishing 5 groups, viz. pre-eclampsia, essential hypertension, chronic nephritis, uncomplicated hypertension of pregnancy, and eclampsia (Table I).

TABLE I

	Pre-eclampsia	*Essential Hypertension*	*Chronic Nephritis*	*Uncomplicated Hypertension of Pregnancy*	*Eclampsia*	*Total*
Number of cases	86	12	4	16	2	120
Average duration of treatment (days)	7·4	11·1	29·5	6·7	3·5	11·6
Response to treatment						
Good	76	8	4	16	2	106 (88·3%)
Fall in B.P., then rise	4	1	—	—	—	5 (4·2%)
No response ..	6	3	—	—	—	9 (7·5%)

1. *Pre-eclampsia*

All patients with a blood pressure reading of 140/90 mm. Hg or greater, and/or albuminuria, and/or oedema and excessive weight gain, were classified as pre-eclampsia. Provided that on discharge the blood pressure readings were normal, the urine showed no albumen, and there was no oedema present, the classification remained unaltered.

Oral treatment commenced immediately on admission and the dosage was adjusted to suit each patient. Two tablets of PVS 295 given every 2 hours were usually sufficient to evoke a response within 2-4 hours. When 'PVA retard' was used, doses were given at 6 a.m., 10 a.m., 2 p.m., and 6 p.m., and the amounts varied from a maximum of 5-3-3-5 tablets to a minimum of 1-½-½-1 tablets.

Fig. 1 shows a typical response in a 17-year-old primigravid patient with moderately severe pre-eclampsia at the 36th week of pregnancy. PVS 295 was used until a response was obtained, and then the long-acting form was introduced. Within 3 days spontaneous labour commenced and the infant

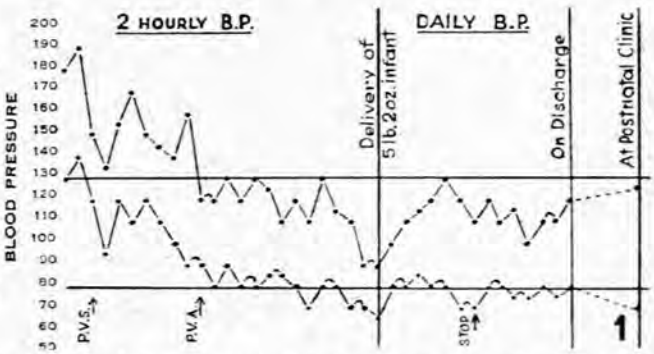

Fig. 1. A typical response to treatment. Pre-eclampsia in a primigravida aged 17 years.

was delivered by forceps because of foetal distress. Treatment was continued for 6 days in the puerperium. On discharge and at the postnatal clinic, the blood pressure readings were normal. The oedema and albuminuria diminished during treatment and disappeared in the puerperium as would be expected.

Of the 86 patients in the pre-eclampsia group, 66 (77%) were considered as moderately and severely affected, but only those with severe symptoms were sedated, so that the effect of protoveratrine alone could be assessed even in this type of patient.

In Table II the patients in this group are listed according to duration of pregnancy at the onset of treatment. The response

* Paper presented at the 42nd South Africa Medical Congress (M.A.S.A.), East London, September-October 1959.

obtained and the maturity of the infants at delivery are shown. It will be noted that 32% of the infants, were premature at delivery (under 5 lb. 8 oz.,) suggesting that although

TABLE II. PRE-ECLAMPTIC PATIENTS TREATED WITH PROTOVERATRINE

Duration of Pregnancy at Onset of Treatment	*Number of Patients*	*Good Results*	*Infants at Delivery*	
			Mature	*Premature*
28 and 29 weeks ..	4	3	1	3
30 and 31 weeks ..	3	3	—	3
32 and 33 weeks ..	15	14	5	10
34 and 35 weeks ..	10	6	3	7
36 and 37 weeks ..	24	22	21	4
38 and 39 weeks ..	15	14	15	1
40 weeks	15	14	15	0
Totals	86	76	60	28
Percentages ..		88%	68%	32%

peripheral and possibly normal uterine blood flow may have been restored by the vasodilatory action of protoveratrine, the placenta was unable to function so as completely to satisfy the needs of the growing foetus. This was particularly so where the toxaemia occurred from the 28th to the 35th weeks of pregnancy; 82% of premature infants were born of mothers in whom pre-eclampsia commenced in or before the 35th week.

2. *Essential Hypertension*

All patients with a history of previous hypertension and with hypertension in early pregnancy, but no albuminuria or oedema were classified as essential hypertension.

The same routine treatment was carried out as for pre-eclampsia. Two of the 12 patients refused to continue with treatment and left hospital undelivered.

3. *Chronic Nephritis*

In 4 patients the diagnosis of chronic nephritis was established after full investigation. In spite of a good blood-pressure response to treatment, abortions occurred in 3 patients and the 4th was delivered of a premature infant after spontaneous onset of labour. Two of the mothers were subsequently transferred to the medical ward of a general hospital for continued treatment and investigation.

4. *Uncomplicated Hypertension of Pregnancy*

This group of 16 patients comprised women who, on admission, were found to be hypertensive without albuminuria, oedema or excessive weight gain. They had no symptoms or signs of pre-eclampsia, and the raised blood pressure returned to normal before discharge. No evidence of hypertension of early pregnancy was available during antenatal attendance at the clinic. Of these patients, 2 developed a raised blood pressure in the middle trimester of pregnancy, 10 showed hypertension in later pregnancy and labour, and 4 required protoveratrine in the puerperium for an unexpected rise in blood pressure.

5. *Eclampsia*

Only 2 cases of eclampsia were treated. Both these patients were unbooked emergency cases and in neither had any antenatal care been given. Both were young primigravidae in whom convulsions had occurred before admission. Heavy sedation was given, followed by protoveratrine.

Although a good blood-pressure response was obtained in both patients and no further convulsions occurred, one developed a renal 'shut down' which required hypertonic intravenous glucose and Bull's intragastric-fluid therapy before diuresis and recovery were established. Both mothers survived and were discharged in satisfactory condition.

Response to Treatment

A good response, i.e. blood pressure decreased to below 130/80 mm. Hg and maintained below this level, was achieved in 106 (88%) of patients (Table I). In 5 (4%) the response could not be maintained and the blood pressure rose again (temporary response). In 9 patients (7·5%) no response was obtained.

No patient on treatment developed eclampsia and no maternal deaths attributable to the administration of protoveratrine occurred.

Side-effects

The commonest side-effects noted were nausea and vomiting. Of the 120 patients treated, 15 (12·5%) showed vomiting, which was easily controlled by a reduction in dosage. This is a markedly lower percentage than that noted in European patients treated with protoveratrine for persistent hypertension.

Excessive dosage resulted in marked hypotension in only 3 (2·5%) patients. Ephedrine hydrochloride, gr. ½ administered by intramuscular injection, successfully overcame this and treatment continued at a reduced dosage.

Cessation of treatment because of side-effects was only necessary in 4 (3·3%) patients.

Foetal Results

These are shown in Table III. The total foetal loss of 22, was made up of 11 stillbirths and 11 neonatal deaths. Six

TABLE III. FOETAL RESULTS

	Pre-eclampsia	*Essential Hypertension*	*Chronic Nephritis*	*Uncomplicated Hypertension of Pregnancy*	*Eclampsia*	*Total*	
						Mat.	*Prem.*
Number of infants	88	11	1	16	3	79	40
Live births ..	79	10	1	16	2	75	33
Stillbirths ..	9	1	—	—	1	4	7
Neonatal deaths..	8	1	—	1	1	2	9
Total foetal loss ..	17	2	0*	1	2	22 (18·5%)	

* Excluding 3 abortions at 20, 24 and 24 weeks of pregnancy.
Mat. = mature. Prem. = premature.

infants were lost owing to factors not directly attributable to the hypotensive treatment, as follows: 1 showed gross changes of hydrops foetalis; 2 died of acute bronchopneumonia in the neonatal period; 2 died of cerebral haemorrhage, 1 died of asphyxia after rupture of the uterus.

Of the remaining 16 infants, representing a foetal loss of 13%, 14 were premature and the causes of death were ascertained as follows: intra-uterine death, 6; concealed accidental haemorrhage, 2; abruptio placentae in the second stage of labour, 1; prematurity with no other cause of death found at post-mortem, 7. These infants died within 48 hours of delivery. The 2 full-term infants lost were macerated twins.

COMMENTS AND CONCLUSIONS

Puroverine, as used in this series, proved to be a potent hypotensive agent, controlling 88·3% of cases of hypertension

in pregnancy irrespective of the underlying pathological changes which had resulted in the raised blood pressure.

The management of toxaemia of pregnancy by this means has not materially altered the natural course of the disease. Apart from the significant facts that no patient developed eclampsia and no death occurred from pre-eclampsia, the relatively high proportion of premature infants delivered does indicate that placental function was not significantly improved.

The successful control of hypertension by the oral administration of puroverine has reduced the need for heavy sedation with barbiturates, paraldehyde and morphine, with their attendant disadvantages. The patients have been conscious and able to take nourishment and fluids, which would have previously required intravenous administration.

The side-effects of the preparation are unpleasant, but only necessitated cessation of therapy in a very small percentage of patients. Overdosage had no serious consequences; in the 3 patients who developed hypotension, ephedrine hydrochloride, gr. $\frac{1}{2}$ by intramuscular injection, rapidly restored the blood pressure to a normal level.

The conclusion that puroverine is a useful and safe adjunct to the treatment of hypertension of pregnancy appears to be justified.

Although the vasodilatory effect should produce increased blood flow and oxygenation of tissues including the placenta, the prematurity rate of one-third indicates that the pathological process has not been halted. We are not much closer to the understanding of the aetiology of pre-eclampsia. Continued clinical observation, careful judgment and termination of pregnancy as required has not been supplanted by the hypotensive effect of this drug, nevertheless, it is a safe means of control of raised blood pressure until delivery can be effected by the procedure of the practitioner's choice.

SUMMARY

1. 120 patients with hypertension in pregnancy were treated with protoveratrine (puroverine-Sandoz PVS 295, and PVA) both the short-acting and the retard forms being used.

2. Patients were divided into the following 5 groups: pre-eclampsia; essential hypertension; chronic nephritis; uncomplicated hypertension of pregnancy; eclampsia.

3. Good hypotensive response was obtained in each group, in the series as a whole it was satisfactory in 88·3% of patients.

4. The side-effects of the preparation are unpleasant, but are easily controlled in the great majority of patients by simple reduction of dosage.

5. Although the vasodilatory effect should produce increased blood flow and oxygenation of tissues including the placenta, the prematurity rate of 32% indicates that the pathological process is not significantly altered.

6. Continued clinical observation, careful judgment, and termination of pregnancy as required, have not been made unnecessary by protoveratrine, which, however is a safe means of control until delivery can be effected by the procedure of choice.

REFERENCES

1. Käser, O. (1953): Gynaecologia (Basel), **125**, 259.
2. Krupp, P. J., Farris, C., Pierce, C. F. and Jacobs, A. (1954): Amer. J. Obstet. Gynec., **68**, 1118.
3. Farris, C. and Krupp, P. J. (1957): *Ibid.*, **74**, 1043.
4. Morris, N. (1955): J. Obstet. Gynaec. Brit. Emp., **62**, 696.
5. Winkler, E. G. and Cangello, V. W. (1958): Amer. J. Obstet. Gynec., 75, 433