ALPHA-METHYL DOPA (ALDOMET) AS A HYPOTENSIVE AGENT IN THE TREATMENT OF TOXAEMIAS OF PREGNANCY

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There is controversy regarding the routine use of hypotensive agents in the treatment of toxaemias of pregnancy. Dieckmann and Harrod (1958) claimed that the use of hypotensive therapy, together with other measures such as rest and induction of labour, enabled them to lower their perinatal mortality and the incidence of cerebro-vascular accidents. They stressed, however, that the foetal survival rate was not necessarily improved just because the blood pressure was lowered, and that there was no significant decrease in proteinuria or abruptio placentae in their treated cases. Carey (1964) found no evidence to show that the employment of hypotensive therapy reduced the perinatal mortality in toxaemia of pregnancy. It was, however, valuable in protecting the mother by reducing the caridac load and the risk of cerebral haemorrhage.

Controversy has also arisen with regard to the type of hypotensive agent that is best for the mother and the foetus. Alpha-methyl dopa ("Aldomet", Merck, Sharpe, and Dohme) is one of the most popular drugs in the treatment of non-pregnant hypertensives (Bayliss and Harvey-Smith, 1962; Daly and Evans, 1962; Irvine, *et. al.*, 1962; Hamilton and Kopelman, 1963; Smirk, 1963; Toh and Lim, 1966).

The main object of the present investigations is to assess the hypotensive potency of Aldomet in the treatment of moderate and severe toxaemias of pregnancy (pre-eclamptic toxaemia, essential hypertension and renal hypertension).

MATERIALS AND METHODS

All cases of moderate and severe toxaemias of pregnancy were included in this study. From June 1964 to December 1966, 31 cases of toxaemias of pregnancy were admitted and treated with Aldomet in the ante-natal ward of the University Unit at Kandang Kerbau Hospital, Singapore.

The scheme of management was as follows:

Every case of toxaemia of pregnancy on admission was given phenobarbitone orally, gr. 1 twice a day (at 8 a.m. and 2 p.m.) together with sodium amytal gr. 3 at night. If there was gross oedema, a diuretic (chlotride) was also given. The patients were advised to rest in bed and were given salt restricted diets.

Biochemical and microscopic examination of the urine, renal concentration and dilution tests, and the blood urea level, were determined on admission.

The patients were put on a careful fluid intake and output chart. They were weighed twice a week and the blood pressure was recorded in the supine position at 6 a.m. 12 noon, and at 6 p.m.

Twenty-four hours after admission, if (a) labour was not induced or the patient was not already in labour, and (b) the blood pressure was still 150/100 mm of mercury or above, Aldomet was started. The initial dose was 1 tablet (250 mg) three times a day (at 8 a.m., 2 p.m., and 8 p.m.). The dose was adjusted every other day by the addition of 1 tablet daily until an adequate response was achieved. The maximum dose was 750mg. three times a day.

A close watch was kept on the side effects of the drug, including giddiness, nausea, diarrhoea, vomiting, depression, pyrexia, liver damage and blood dyscrasia.

The newborn babies were carefully examined for any evidence of toxic effects or congenital abnormalities.

RESULTS

The hypotensive response

The hypotensive response to therapy is shown in Table 1 and IA. The diagnosis of the type of toxaemia of pregnancy was based on the clinical history, physical examination and the results of the laboratory investigations. The cases included Essential Hypertension, Pre-eclamptic Toxaemia, Renal Hypertension, and the group of Pre-eclamptic toxaemia superimposed on essential hypertension. A good response was seen in about 60% of the

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TABLE I

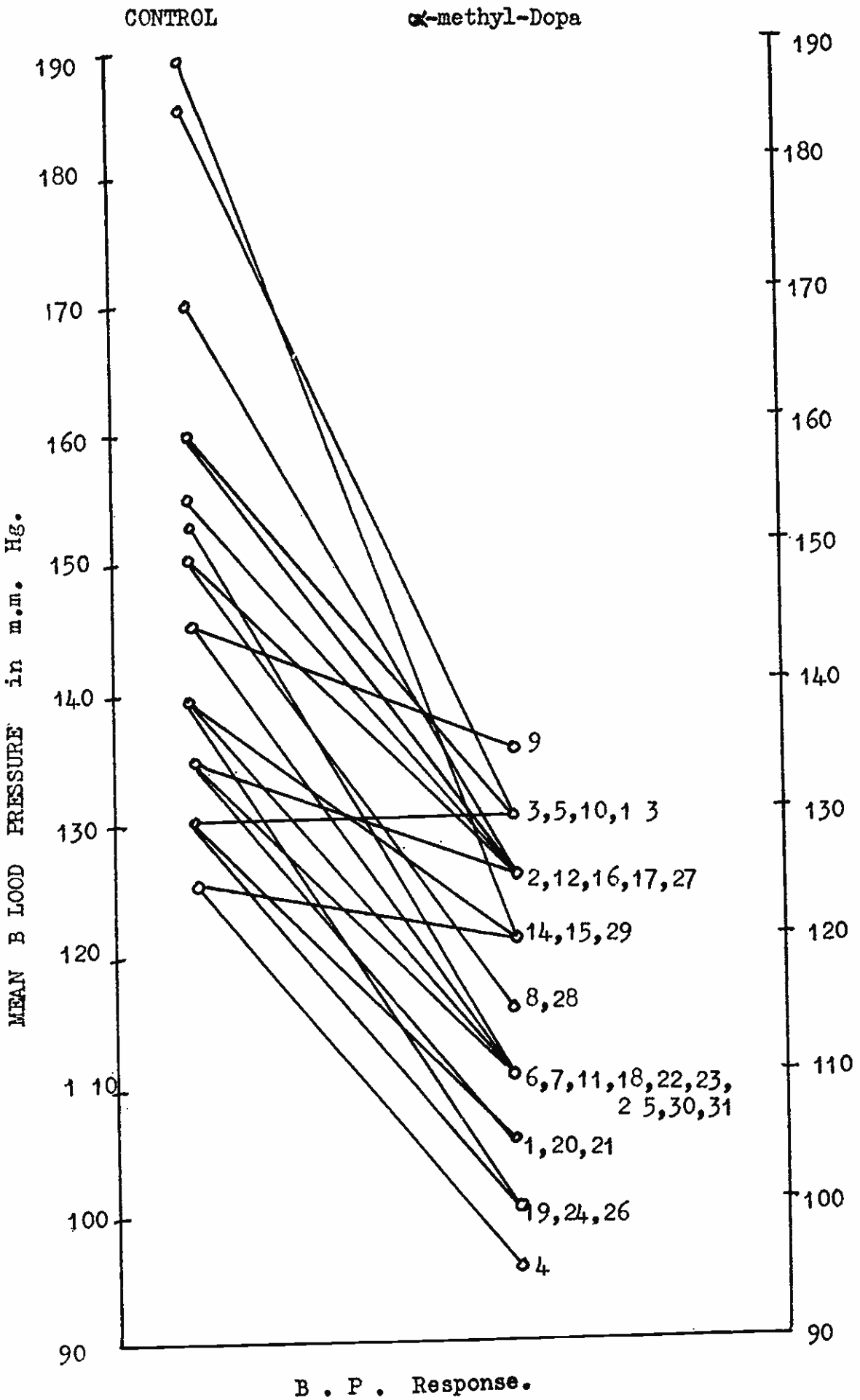
No.	Age	Parity	Diagnosis	Blood pressure Initial	Final	(supine) Fall	Result	Dosage 8 am	2 pm	9 pm
1	33	5	Ess. Hypert.,	170/100	130/80	40/30	Good	3	2	3
2	30	1	P.E.T.	160/110	150/100	10/10	Poor	2	1	2
3	40	2	Ess. Hypert.	160/100	160/100	0	Poor	3	2	3
4	40	3	P.E.T.	150/100	110/80	40/20	Good	1	1	1
5	37	7	Renal Hypert.	200/120	160/100	40/20	Fair	2	2	2
6	28	1	P.E.T.	180/110	130/90	50/20	Good	2	2	2
7	36	7	P.E.T. on E· Hypt.	180/125	130/90	50/35	Good	1	1	1
8	37	0	Ess. Hypert.	185/115	140/90	45/25	Good	2	2	2
9	39	3	P.E.T.	180/110	160/110	20/0	Poor	1	1	2
10	36	4	P.E.T. on E. Hypt.	220/150	150/110	70/40	Fair	3	3	3
11	38	5	Ess Hypert.	160/100	130/90	30/10	Good	1	1	1
12	35	8	Ess. Hypert.	200/120	160/90	40/30	Fair	3	2	3
13	44	10	Ess. Hypert.	170/100	170/90	0/10	Poor	2	2	2
14	28	1	P.E.T.	150/100	140/100	10/0	Poor	1	1	1
15	32	8.	P.E.T. on E. Hypt.	240/140	140/100	100/40	Fair	3	2	3
16	26	0	P.E.T.	200/120	150/100	50/20	Fair	3	2	3
17	38	7	Renal Hypert.	200/140	150/100	50/40	Fair	1	1	1
18	45	10	Renal Hypert.	150/100	120/90	30/10	Good	1	1	2
19	34	4	P.E.T.	170/120	120/80	50/40	Good	2	2	2
20	37	11	Ess. Hypert.	150/100	130/80	20/20	Good	2	1	2
21	36	2	P.E.T.	160/100	120/90	40/10	Good	2	1	2
22	38	6	P.E.T.	150/100	130/90	20/10	Good	2	2	3
23	33	6	P.E.T.	150/110	140/80	10/30	Good	1	1	1
24	35	6	P.E.T.	150/100	120/80	30/20	Good	1	1	2
25	35	3	Ess. Hypert	160/110	135/90	25/20	Good	2	2	3
26	34	3	P.E.T.	160/100	125/80	35/20	Good	1	1	2
27	39	7	Ess Hypert	200/110	160/90	40/20	Fair	2	2	3
28	32	3	P.E.T.	185/110	140/90	45/20	Good	2	2	2
29	35	2	Renal Hypert.	180/100	150/90	30/10	Fair	2	2	2
30	30	2	P.E.T.	170/105	140/80	30/25	Good	2	1	2
31	25	0	P.E.T.	160/110	130/90	30/20	Good	2	1	2

Good response: Blood pressure maintained within 140/90 mm. of mercury.

Fair response: Blood pressure still above 140/90, but the diastolic pressure falls by 20 mm. of mercury or more.

Poor response: Blood pressure above 140/90 and the diastolic fall is less than 20 mm. of mercury.

TABLE IA


CONTROL
α-methyl-Dopa
190
180
170
160
150
140
130
120
110
100
90
MEAN BLOOD PRESSURE in m.m. Hg.
9
3,5,10,13
2,12,16,17,27
14,15,29
8,28
6,7,11,18,22,23,
25,30,31
1,20,21
19,24,26
4
B . P . Response.

cases treated. Table II shows a summary of the response in relation to the type of toxaemia of pregnancy studied.

TABLE II

	Response			
	Good	Fair	Poor	Total
Essential Hypertension	5	2	2	9
P.E.T. on Essential Hypert	1	2	0	3
Pre-eclamptic toxaemia	11	1	3	15
Renal Hypertension	1	3	0	4
Total	18	8	5	31
	(58%)	(26%)	(16%)	

The Duration of Therapy

Most of the cases had a rather short duration of therapy of 2 to 3 weeks before the termination of pregancy. Cases with essential and renal hypertension when diagnosed early in pregnancy had longer durations of therapy. The duration of therapy is shown in Table III below.

TABLE III

Weeks of therapy	No. of cases
1	4
2	8
3	11
4	4
5	2
6 and more	2

The maturity at delivery

In the cases studied, the maturity aimed at was 36 weeks. However, in some cases termination of pregnancy had to be considered at or after the 32nd week of gestation, depending on the clinical state of the mother and the foetus. The hypotensive response was one of the determining factors. Evidence of foetal growth retardation, persistent proteinuria, and accidental haemorrhage were other criteria for termination of pregnancy. Good obstetrical judgement is the most important single factor determining the maternal and foetal mortality.

Method of delivery

The method of delivery of the various cases treated were as follows:

Spontaneous vaginal delivery	8 cases
Surgical induction & Vaginal delivery	16 cases
Surgical induction & Caesarean Section	4 cases
Elective Caesarean Section	3 cases

Side effects

Except for occasional giddiness and nausea no other side effects were noted. Transient drowsiness and insomnia at night are believed to be common side effects (Toh and Lim, 1966), but since our patients were already on sedatives and hypnotics, these side effects could not be assessed.

No toxic signs or foetal malformations were noted.

Perinatal and maternal mortality

Twenty of the 31 babies were born in satisfactory state. Nine were noted to be feeble at birth. There were 2 macerated stillborns, one weighing 2 pounds 8 ounces and the other weighing 2 pounds 14 ounces. Two premature babies (3 pounds and 3 pounds 10 ounces) that were feeble at birth died within the first 7 days of delivery. The perinatal mortality rate in the present study was 129 per thousand as compared to the rate of 28.8/1000 at the Kandang Kerbau Hospital (Wong 1965).

There were no maternal deaths in the present study.

DISCUSSION

The exact mechanism of action of Aldomet is not well understood. Aldomet acts as a competitive antagonist in blocking the conversion of Dopa (Dihydroxy-phenylalanine) to Dopamine (Dihydroxy-phenylethylamine) which is the precursor of the catechol-amines, adrenalin and nor-adrenaline. The drug also inhibits the decarboxylation of tyrosine, phenylalanine, and 5-hydroxy tryptophan. It probably also causes depletion of 5-hydroxy tryptamine in the brain. Aldomet appears to be an ideal hypotensive because of the following qualities (Toh and Lim, 1966):

It lowers the recumbent as well as the standing blood pressure.

It has minimal side effects.

Tolerance does not develop.

Absorption is good and uniform.

The other hypotensive agents appear to be ineffective or unsuitable bcause of serious side effects. The ganglion blocking agents have unpleasant parasympathetic side effects. The rauwolfia alkaloids are weak hypotensives and take as long as two weeks to achieve a response. The protoveratrines appear to be used with frequency in the management of toxaemias of pregnancy (Dieckmann and Harrod, 1958;

Elliot, 1959; Carey, 1964), but they have troublesome side effects, since the therapeutic and toxic doses are almost the same. Guanethedine has been thought to be a good agent for the treatment of hypertension for ambulatory patients (Burnett, 1962), but postural hypotension makes the drug unsatisfactory for pregnant mothers. Hydrallazine produces satisfactory drops of blood pressure in severe toxaemias of pregnancy (Johnson and Clayton, 1957; Johnson and Thompson, 1958; Ratnam and Sivasamboo, 1966). However, tolerance to hydrallazine develops rapidly so that the drug is only effective for short term therapy, when the object is to control the blood pressure just before delivery.

In the present series, Aldomet, in combination with sedatives and diuretics, appears to produce satisfactory falls of blood pressure in toxaemias of pregnancy. Tolerance does not develop and therefore long term therapy was possible. The hypotensive response was found to be good in 18 cases (58%), fair in 8 cases (26%) and poor in 5 cases (16%). The response does not appear to be influenced by the type of toxaemia. Carey (1964) observed that Aldomet produced satisfactory hypotensive effects in only about one-third of cases with pre-eclamptic toxaemia.

The perinatal mortality in the present study was 12.9% and the high perinatal mortality is in accordance with other observations (Carey, 1964; Lewis, 1964; Barnes, 1965) that lowering the blood pressure per se may not significantly reduce the perinatal mortality. The main purpose of controlling the blood pressure appears to be the protection of the mother from the complications of severe and prolonged hypertension, particularly the prevention of cardiac failure and cerebral haemorrhage. Furthermore, in cases of chronic nephritis or essential hypertension, the control of the blood pressure may prevent superimposed pre-eclamptic toxaemia in late pregnancy.

SUMMARY

Thirty-one cases of severe toxaemias of pregnancy were given Aldomet as a hypotensive agent. The response was found to be geod in 18 cases (58%), fair in 8 cases (26%), and poor in 5 cases (16%).

The advantages of Aldomet over other hypotensive agents were discussed.

The side effects of the drug were found to be minimal.

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