Prolonged Use of Methyldopa in Severe Hypertension in Pregnancy

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Although methyldopa has been widely used as a hypotensive drug for several years, little has been written about its use during pregnancy. Hans and Kopelman (1964) used this drug for short periods in pre-eclamptic toxæmia with apparent benefit.

Treatment with hypotensive drugs may be imperative for the safety of the mother when manifestations such as retinal haemorrhages develop during pregnancy. Even in malignant hypertension a successful pregnancy is possible when the blood-pressure is controlled (Kincaid-Smith *et al.*, 1958). If there is no clear-cut indication that the mother requires treatment, interest centres around the possibility that hypotensive drugs may improve the outlook for the foetus. Presumably the foetus and the placental circulation derive the maximum benefit from treatment begun early in the pregnancy. In this paper we report our experience with the long-term use of methyldopa in hypertensive pregnant women.

Clinical Material and Method of Treatment

Thirty-two patients with severe hypertension were treated with methyldopa during pregnancy. The details are given in Table II. Three patients had had blood-pressure readings taken only during pregnancy; the remainder were known to be hypertensive when they were not pregnant (Table II). Twenty-five patients had had previous pregnancies, all but two having been hypertensive during pregnancy, and 15 of them had had previous unsuccessful pregnancies.

Even before treatment was begun the blood-pressure level during pregnancy was usually lower than that recorded before or after the pregnancy (Table II). The patients were a heterogeneous group and about a third had known or presumed underlying renal disease. We did not include those with pre-eclamptic toxæmia alone, but in 12 patients pre-eclamptic toxæmia probably developed as a complication.

Two patients were treated throughout the whole pregnancy, and most were treated for periods of three to six months. In five the drug was used in the first trimester (Table II).

Methyldopa was the only hypotensive drug used in most patients, but seven also received reserpine or chlorothiazide at some time during the pregnancy. The initial dose of methyldopa was usually 0.25 g. daily, and this was increased in an attempt to maintain the blood-pressure at 140/90 or lower in the standing position. The final total daily doses ranged from 0.5 to 4 g.

Results of Treatment

Table II shows the details of treatment and the outcome of the pregnancy. The blood-pressure was usually satisfactorily controlled. The difference between the blood-pressures immediately before treatment was started and those taken at the midpoint of treatment were highly significant (Table I).

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TABLE I.—Difference in Blood-pressures Immediately Before Treatment and Those Taken at the Mid-point of Treatment

	Systolic B.P.	Diastolic B.P.
Number of patients	29	29
Mean difference	36.6	24.7
Standard error	3.33	2.38

So far as was possible treatment was carried out on an out-patient basis and patients were admitted to hospital only if the blood-pressure was difficult to control or if they developed other abnormalities such as oedema or proteinuria.

Foetal Mortality and Morbidity.—The babies were examined by members of the obstetric staff of the hospital, and premature babies or those with any apparent abnormality were seen by a paediatrician. No significant abnormalities were noted in this group. Four babies had umbilical herniae, and one was noted to have slight clitoral enlargement. One baby who had cyanotic attacks had a systolic cardiac murmur, which after cardiological investigation was stated to be functional. Two patients who developed superimposed pre-eclamptic toxæmia before the 30th week lost their babies; one of these was stillborn and the other died after a few hours (foetal weight 700 g.). One patient, who habitually lost her baby at about the same stage of pregnancy, had a foetal death *in utero* after premature rupture of the membranes at 27 weeks.

Pre-eclamptic Toxæmia.—It may be very difficult to assess the onset of pre-eclamptic toxæmia in a group of patients who are already hypertensive and some of whom have proteinuria. However, in 12 patients we made a diagnosis of pre-eclamptic toxæmia on the basis of an increase in or appearance of proteinuria or oedema or because of a sudden increase in hypertension. The serum uric-acid level was sometimes of value in confirming this diagnosis (Table II). We did not obtain any clear-cut improvement in the pre-eclamptic toxæmia as a result of methyldopa treatment in these patients. Bed rest, together with an increased dose of methyldopa, controlled the hypertension and at the same time the proteinuria sometimes decreased or disappeared. However, the persistence of a high serum uric acid, retinal arterial narrowing, and, in some instances, proteinuria seemed to indicate that lowering the blood-pressure with methyldopa did not counteract the basic abnormality of pre-eclamptic toxæmia.

Side-effects and Withdrawal of Methyldopa.—No serious side-effects were encountered, but several patients complained of drowsiness. Methyldopa was discontinued in one patient at 29 weeks because the blood-pressure had fallen too low. This patient had been on reserpine and chlorothiazide before the pregnancy, and methyldopa had been added to achieve better control of the blood-pressure (Case 10).

Discussion

Our main purpose in reporting our experience with methyldopa is to record that it is an effective hypotensive agent in pregnancy hypertension. There is probably some advantage in treating subjects as out-patients, because methyldopa is relatively more effective when the patient is in the upright position. The freedom from side-effects or severe postural hypo-

TABLE II.—Summary of Cases

No.	Age	Parity	Hypertension or Toxaemia in Previous Pregnancy	Available Random B.P. Readings when Not Pregnant (Off Treatment)	Associated Renal or Other Disease	Antenatal B.P.		Duration of Treatment	Weeks of Gestation	Duration of Pregnancy (Weeks)	Method of Delivery	Foetal Result	Foetal Weight (g.)	Proteinuria during Pregnancy	Oedema during Pregnancy	Blood Urea (mg./100 ml.)	Uric Acid
						Immediately before Treatment	At Mid-point of Treatment										
1	24	P 1 + 1	No	210/130	Diabetic glomerulosclerosis	210/110	150/90	18	36	36	C	Living	2,608	+	-	31	-
2	39	Primip.	Hypertension in 2	190/130		190/120	130/85	28	37	37	C	"	2,300	-	+	26	-
3*	39	P 2 + 2, 1 NND		180/115		185/110	130/80	20	38	38	C	"	2,212	-	+	29	7.2
4*	20	Primip.	No	150/110	Habitual abortion	160/110	150/90	22	34	34	I	"	1,700	+	+	35	7.7
5	31	P O + 4		190/130		150/115	140/100	16	29	29	S	S.B. premature rupture membranes	1,700	-	+	16	-
6*	37	P 7 + 3	Hypertension in 3, Proteinuria in 2	160/110	P.H. pyelonephritis. Urine infected in present pregnancy	170/100	140/90	21	38	38	C	Living	2,610	+	+	18	5.1
7	26	Primip.	Hypertension	180/110		160/100	135/95	16	40	40	I	"	4,330	-	+		
8	27	P 1		180/120		170/115	120/80	0	12	42	S	"	4,800	-	+		
9*	45	P 5 + 1	Hypertension in 4	190/130		220/120	(39 weeks)	37	42	30	I	"	1,024	-	+		
0	27	P 3	"	180/120	Chronic pyelonephritis	170/100	100/50	20	32	39	S	S.B. Living	3,250	+	+	33	6
1*	21	Primip.	Hypertension in 2	160/100		160/100	130/80	33	37	37	I	"	1,843	+	+	36	-
12	27	P 2	Hypertension	180/120	P.H. pyelonephritis	160/90	140/85	13	40	40	I	"	4,330	-	+		
13	34	P 1 (S.B.)	Hypertension	180/130		150/110	130/90	25	38	38	I	"	2,610	-	+		
14	40	P 5 + 1	Hypertension in 2, Toxaemia in 1	180/110		170/100	130/80	26	40	40	S	"	3,490	-	+		
15	32	P 3 (1 IUD)	Toxaemia in 2	160/115		170/100	130/70	27	38	38	I	"	4,400	-	+		
16	30	P 4 (1 S.B.)	Hypertension in 4	190/130		190/150	140/90	18	24	42	C	"	4,260	-	+	17	6
17	39	P 7	"	190/120		170/100	130/80	26	40	40	I	"	3,246	-	+	30	3.2
18	36	P 1 + 1	"	220/110		170/100	130/80	0	38	38	I	"	2,640	-	+	40	
19*	30	P 2	"	195/145	Proteinuria	170/130	100/70	35	38	39	I	"	1,775	1	+		
20*	30	P 1	Hypertension	180/120		170/130	130/90	0	38	38	I	"	2,470	+	+	37	9.5
21	40	P 3 (1 S.B.)	Hypertension in 3	150/85		140/110	140/90	14	36	36	I	"	2,080	-	+	37	8.8
22	27	P 1 + 1	"	160/110	Familial G.N. Post-streptococcal G.N. on biopsy	160/110	130/80	6	39	39	I	"	3,570	-	+	32	-
23	28	P 3	"	180/120	P.H. nephritis	160/100	115/65	6	41	41	I	"	3,220	-	-	16	2.4
24	23	P 1	Hypertension	180/110	Familial G.N. Sister of Case 22	180/115	140/90	12	37	37	I	"	2,810	-	-	29	
25*	30	P 1 (S.B.)	"	150/110	Chronic lobular post-streptococcal G.N. (biopsy)	180/110	130/80	16	36	36	C	"	2,130	+	+	39	5.1
26	31	P 4 (1 S.B.)	Hypertension in 3	170/115		150/110	135/85	27	40	40	I	"	3,810	-	+	26	3.8
27*	27	Primip.	Hypertension in 3	180/100		150/100	135/85	30	34	34	I	"	1,835	-	+	26	7.1
28	39	P 3 (1 S.B.)	"	160/100	Chronic pyelonephritis	190/110	130/80	15	38	38	S	"	3,120	-	-		
29	29	Primip.	Hypertension in 1	Not known		180/110	160/90	32	37	37	I	"	2,000	+	+	32	
30*	39	P 3	"	"		180/120	130/90	27	32	32	I	"	700	-	+	40	
31*	34	P 6	Hypertension in 3, Proteinuria in 2	170/110	Proteinuria	165/100	120/80	23	36	36	I	"	3,100	+	-	35	7.4
32	34	Primip.	"	Not known		160/100	120/80	24	39	39	S	"	3,170	-	+		

* Pre-eclamptic toxæmia. † On treatment before and throughout pregnancy. C = Caesarean section. S = Spontaneous delivery. I = Surgical induction. G.N. = Glomerulonephritis. P.H. = Past history

tension permitted easy regulation of the blood-pressure in out-patients.

Since the thalidomide disasters both doctors and mothers are understandably hesitant about the use of a new drug during pregnancy. It is therefore reassuring that we found no evidence of ill effects on the foetus in patients treated in the first trimester or with doses of methyldopa up to 4 g. daily.

The perinatal mortality rate of 9.3% does not seem excessive for this group of severely hypertensive women, particularly as one of the three foetal deaths was thought to be unrelated to the hypertensive disease, which reduces this figure to 6.2%. Townsend (1958), studying a similar population group in Melbourne, found a perinatal mortality of 16% when mothers had an initial diastolic pressure of 110 mm. Hg, and this figure rose to 50% in patients in whom this degree of hypertension was complicated by proteinuria. Twelve of our patients had proteinuria, including the two who lost their babies as a result of developing pre-eclamptic toxæmia before the thirtieth week.

As MacGillivray (1964) has pointed out, only a careful controlled trial will establish whether hypotensive drugs increase the rate of successful pregnancies in hypertensive mothers.

We are now conducting a controlled trial of methyldopa in pregnancy hypertension because we feel that it has definite practical advantages as well as the possible theoretical advantage of inhibition of decarboxylase (*Brit. med. J.*, 1964).

Summary

Methyldopa has been used to control hypertension in pregnancy for periods up to the whole gestation time without any apparent adverse effect on the foetus.

The blood-pressure can usually be easily controlled on an out-patient basis and side-effects were minimal.

Only 3 out of 32 severely hypertensive women lost their babies, and as one foetal death was due to premature rupture of the membranes the corrected perinatal mortality rate was only 6.2%.

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Trial of Ambilhar, a Nitrothiazole Derivative, in *S. mansoni* Infections in Tanzania

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The schistosomicidal action of Ambilhar† (a nitrothiazole derivative, 1-(5-nitro-2-thiazolyl)-2-imidazolidinone) in mice infected with *Schistosoma mansoni* was reported by Lambert (1964). Preliminary observations of its use in man were recorded by Jordan (1966a), and the present communication reports parasitological findings obtained four months after treatment.

Methods and Materials

The use of the percentage reduction in egg load was suggested by Jordan and Randall (1962) for assessing results of suppressive therapy in *Schistosoma haematobium* infections, and Bradley (1963) showed that the "cure rate" in this infection was inversely proportional to the initial egg output. Bell (1964) outlined the advantages of using the former parameter of chemotherapeutic activity of schistosomicidal drugs and devised a new method for the necessary quantitative studies in relation to *S. mansoni* infections (Bell, 1963). This method was used in the present trials. Bell (1964) stressed that a 100% reduction in egg load (by the filtration-staining technique) does not in fact imply a cure, but merely an egg output of less than 1,000 eggs a day. Within this context "cure rates" are given for results obtained by the filtration-staining technique. On the other hand, this method, combined with further stool examinations and the use of other techniques, more closely approaches what may be necessary to evaluate a true parasitological cure, and when three techniques have been used and three or four

stools examined the absence of evidence of *S. mansoni* is considered for the purpose of this communication to represent a cure.

Children and adults excreting eggs of *S. mansoni* were treated in these trials. The former were found infected in school surveys; the latter requested treatment—invariably complaining of abdominal pain—and on investigation were found to be infected. All patients were treated as in-patients with a dose of 25 mg./kg. body-weight daily (in two doses) for five days.

Prior to treatment patients were given a general clinical examination, and a 24-hour collection of stool was made for processing by the filtration-staining technique (Bell, 1963) in order to assess the 24-hour output of *S. mansoni* eggs and to give an indication of the intensity of infection.

At follow-up examination two and four months after treatment, patients were readmitted for the collection of a further 24-hour stool for quantitative determination of the egg load, and an additional stool was collected; three 1-g. aliquots were examined for *S. mansoni* eggs by the A.M.S. III technique (Hunter *et al.*, 1948), the rest of the stool being treated for hatching of eggs and examination for miracidia. Thus at the follow-up examinations three or four stools were generally examined and three different techniques were used for the detection of eggs or miracidia.

Results

Comparative results of the quantitative filtration-staining technique two and four months after treatment were obtained

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