Methyldopa Combined with Prindolol in the Treatment of Severe Hypertension

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SUMMARY

In a clinical trial of 30 patients suffering from severe hypertension (diastolic blood pressure above 130 mmHg) the combination of methyldopa and prindolol produced a satisfactory drop in blood pressure; a further 2 patients were satisfactorily controlled with the addition of furosemide 40 mg daily. Side-effects were few, and this trial was characterised by the absence of postural hypotension; this combination did not enhance central nervous system side-effects. A synergistic effect between methyldopa and β-adrenergic blocking agents as regards their hypotensive effect may exist, and the combination may be a better alternative to use than sympatholytic agents such as guanethidine or bethanidine sulphate in the treatment of severe hypertension.

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One of the problems confronting a clinician in the treatment of hypertension is that intolerable side-effects may make the patient feel even worse. Bethanidine sulphate or guanethidine act by depleting the peripheral arterioles of noradrenaline and cause side-effects such as impotence, postural hypotension, giddiness or diarrhoea.[1] Beta-adrenergic blocking agents produce no postural hypotension or sexual disturbance, but have been found to be of value mainly in mild to moderate hypertension.[2,3] Moreover, it is probably unwise to exceed the anti-anginal dose in the treatment of hypertension, viz. propranolol 320 mg daily or prindolol 45 mg daily, because of the cost of therapy and because a further drop in blood pressure (BP) would probably be relatively small.[4] This clinical trial was thus initiated to determine if methyldopa (Aldomet), a hypotensive agent which produces little postural hypotension, could be used effectively with prindolol (Visken) in the treatment of severe hypertension.

PATIENTS AND METHODS

Thirty patients suffering from severe hypertension (initial diastolic BP of 130 mmHg or above) were selected for this trial. Patients who were previously on guanethidine or bethanidine sulphate were taken off their therapy, and once the original diastolic BP was attained (usually between 5 - 7 days) they were put on methyldopa. All patients were initially put on methyldopa 1 g daily (divided dose of 500 mg every 12 hours) for a period of 2 weeks, because methyldopa produces a hypotensive effect quickly, whereas β-adrenergic blocking agents may have a delayed effect.[5] After 2 weeks prindolol (Visken) 5 mg twice daily was added and the dose increased at weekly intervals to a dose that produced a diastolic BP of less than 100 mmHg. Patients suffering from overt manifestations of cardiac failure or bronchial asthma were excluded from the trial. There were 17 Black and 13 Indian patients in this clinical trial—16 females and 14 males.

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RESULTS

At the end of the 3-month trial 28 of the 30 patients were effectively controlled with methyldopa 1 g daily and prindolol in a variable dose. In the 2 patients in whom a diastolic BP of 100 mmHg was not attained, furosemide 40 mg daily produced the required drop in BP. Tolerance was defined as a state in which an increase in the dosage of prindolol became necessary because of a rise in the diastolic BP after a level of 100 mmHg or less had been obtained, and was not seen in any of the patients.

The initial mean arterial pressure (MAP) was 158,3. On therapy with methyldopa the MAP was 138,7. The addition of prindolol produced a MAP of 111,5 (Table I). The median dose of prindolol was 26,3 mg. The mean blood urea before therapy was 44,8 mg/100 ml and after therapy it was 48,9 mg/100 ml (Table II). The pulse rate before therapy was 76/minute, on therapy with methyldopa 74/minute, and with the addition of prindolol 72/minute (Table III). Side-effects of previous hypotensive therapy included drowsiness, postural hypotension, impotence and diarrhoea. A feature of the combination of methyldopa and prindolol was the absence of postural hypotension as a side-effect, and the presence of impotence in only one patient on methyldopa. There did not appear to be any enhancement of central nervous system side-effects when prindolol was combined with methyldopa.

DISCUSSION

This clinical trial was undertaken to determine if the combination of methyldopa and prindolol is effective in the treatment of severe hypertension and without side-effects, such as postural hypotension, which may occur with hypotensive agents like guanethidine or bethanidine sulphate. A previous trial has shown that patients who

TABLE I. MEAN ARTERIAL PRESSURE BEFORE AND AFTER THERAPY (30 CASES)

	Initial mean arterial pressure*	Mean arterial pressure on methyldopa	Mean arterial pressure on methyldopa and prindolol
Mean	**158,33**	**138,66**	**111,49**
Standard deviation	**7,5188**	**6,4640**	**6,7857**
Standard error of mean	**1,3727**	**1,1801**	**1,2388**
		(17,7614)	**(25,4013)**
		***P*<0,001**	***P*<0,001**
		Highly significant	**Highly significant**

* Mean arterial pressure = $\frac{\text{systolic} + 2\ \text{diastolic}}{3}$

TABLE II. BLOOD UREA BEFORE AND AFTER THERAPY

	Blood urea before therapy (mg/100 ml)	Blood urea after therapy (mg/100 ml)
Mean	**44,833**	**48,9666**
Standard deviation	**15,8703**	**16,8778**
Standard error of mean	**2,8974**	**3,0814**
	***P*<0,005**	

TABLE III. PULSE RATE BEFORE AND AFTER THERAPY

	Pulse rate before treatment	Pulse rate on methyldopa	Pulse rate on methyldopa and prindolol
Mean	**76,633**	**74,033**	**72,533**
Standard deviation	**4,9860**	**4,4989**	**5,2962**
Standard error of mean	**0,9102**	**0,8213**	**0,9669**
P	**<0,001**	**<0,001**	**<0,010**
	(6,1963)	**(7,1428)**	**(2,7793)**

did not respond to prindolol were more likely to be patients who had an initial diastolic BP above 130 mmHg.[6] While isolated reports of the combination of methyldopa and prindolol have appeared,[7,8] there was no clear evidence of the value of the combination of methyldopa and β-adrenergic blocking agents in the treatment of hypertension. Previous work on propranolol[9] has shown that: (*a*) its full hypotensive effect may take several weeks; (*b*) the required hypotensive dose of 760 mg was usually greater than the effective anti-anginal dose of 320 mg daily, with a wide fluctuation in dose requirement; and (*c*) it did not produce postural or postexercise hypotension. Methyldopa also produces little postural hypotension,[10] and it was decided to use the drug in combination with prindolol to determine: (*a*) if there was a synergistic hypotensive effect; (*b*) if side-effects of other hypotensive agents could be obviated, especially postural hypotension and sexual disturbance.

Prindolol, a newer β-adrenergic blocking agent, has two important advantages over propranolol: increased dose-for-dose potency and fewer side-effects, particularly a lesser effect on the pulse rate.[4] Animal experiments have shown that prindolol has less of the quinidine effect seen with propranolol.[11] There is conflicting evidence as to the mode of action of prindolol, but it seems that there may be an effect mediated through the central nervous system because of evidence in humans of mental depression, insomnia and vivid dreams as side-effects.[12] There is no explanation for the action of methyldopa. The theory of the false 'neurotransmitter' has been suggested, and it is believed that the decarboxylation of α-methyldopa in the central nervous system is a prerequisite for its hypotensive effect.[13]

This clinical trial showed that methyldopa in a fixed dose of 1 g daily, combined with prindolol in a median dose of 26 mg daily, produced a satisfactory drop in BP. A further 2 patients were effectively controlled when furosemide 40 mg daily was added. Side-effects occurred in 7 patients on methyldopa and in 4 of them drowsiness disappeared after a week. Five patients developed side-effects on prindolol therapy. There did not appear to be any potentiation of central nervous system side-effects, in spite of both these drugs having that potential. No patient developed dizziness or postural hypotension on the combination of methyldopa and prindolol, unlike 5 patients who experienced this side-effect on bethanidine sulphate and 4 patients on guanethidine therapy. A feature of β-adrenergic blocking agents is the absence of any impotence or failure of ejaculation in the male—no patient developed these side-effects on prindolol and only 1 patient developed impotence on methyldopa. There was little effect of the combination of methyldopa and prindolol on the pulse rate, and the initial pulse rate dropped from 76 to 72/minute after therapy. The difference be-

tween recumbent and standing blood pressures was 5 mmHg. The mean rise in blood urea after therapy was only 4 mg/100 ml. Ten patients suffered from renal hypertension, and there was no deleterious effect on therapy.

This clinical trial showed that the combination of methyldopa and prindolol is of value in the treatment of severe hypertension. Previous work has shown the value of combining propranolol with hydralazine,[14] prindolol with a diuretic[7] or hydralazine.[8] It is possible that the combination of methyldopa with the newer β-adrenergic blocking agents may be a suitable alternative to the sympatholitic agents in the treatment of severe hypertension.

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