patient, and is more likely, therefore, to be used in domiciliary nursing in the nurse's absence.

An adequate layer of silicone on the skin is probably more economically obtained by using 100% silicone, for it is more easily seen and the silicone in alcohol tends to run off the patient's back during spraying, carrying the silicone to areas where it is not required. Alcohol is also uncomfortably cold, and we had one patient who refused to continue with the treatment: when we tried the spray on ourselves we had much sympathy for her. The spraying technique can be taught by the nurse to the dullest relative in a few moments.

Summary

Two trials to evaluate the use of silicone sprays in the prevention and treatment of decubitus skin conditions in domiciliary nursing were undertaken in 1961. In the first trial it was found that with patients having normal skin the traditional method used in hospitals for generations was the most effective, but with patients with a skin condition a 5% MS 555 silicone fluid in ethanol was significantly more effective than all other treatments combined (including a 2% MS 555 in ethanol spray). Other evidence that MS 555 fluid is not as inert as other silicone fluids led us to a second trial comparing 100% MS 555 with 100% dimethicone (MS 200 fluid) in freon-operated canisters. The pure MS 555 fluid effectively maintained normal skin in good condition in 14 out of 15 patients and was far more effective in treating established skin conditions (other than areas of actual ulceration, which were not sprayed with either silicone). The pure fluid is probably more economical in use, much more comfortable to the patient than silicone in alcohol sprays, takes only a few seconds to administer, and can more easily be continued by the relatives in the nurse's absence.

It is concluded that pure MS 555 spray is the method of choice in the prevention and treatment of decubitus skin disorders.

We acknowledge the loyal and conscientious work of all the nurses, too many to mention by name, who made this trial possible, and the helpful co-operation of the general practitioners in charge of the patients. Our thanks are also due to Midland Silicones Limited for the supply of silicones; to Mr. R. L. Bass of that company for chemical advice; and to Messrs. Lactagol Ltd., who supplied us with the complete canisters.

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A letter "received by me some 70 years ago from Miss Florence Nightingale" has been left by Colonel Sir William Coates, the physician of Manchester, who died last January aged 101, to his son, Colonel James Coates, "in gratitude for his untiring kindness night and day showed to me in my illnesses." Sir William left £63,919 (£63,160 net; duty £30,470).

ANOTHER HYPOTENSIVE AGENT— METHYLDOPA

BY

DENIS DALEY, M.B., B.Ch.

AND

BYRON EVANS, M.D., F.R.C.P.

United Cardiff Hospitals

There is as yet no ideal drug available for the lifelong treatment of patients with essential or irremediable secondary hypertension. Such a hypotensive agent should have a consistently reliable effect when given by the mouth and there should be no side-effects. After long-continued use tolerance to the drug should not occur, and the patient should feel well and thus encouraged to continue with treatment. In search of this ideal drug the output of new and improved hypotensive agents is so rapid that there is barely time to evaluate one before another becomes available. During the last six months observations have been made on the clinical effects of methyldopa ("aldomet"). It is probable that in the near future it will be combined with other hypotensive agents to produce a better response than when used alone, but the purpose of this investigation was to determine whether methyldopa given alone was of value in the treatment of hypertension.

The mode of action of methyldopa (alpha-methyl-3,4-dihydroxy-1-phenylalanine) in lowering blood-pressure is not fully understood. Several investigators (Sourkes, 1954; Smith, 1959; Oates *et al.*, 1960) have shown that the drug inhibits the decarboxylation of dopa and other amino-acids and thus diminishes the production of noradrenaline and serotonin in the brain and other tissues. It has since been suggested by Gillespie *et al.* (1962) that because methyldopa has a sedative as well as a hypotensive action, properties not shared by other decarboxylating agents, the site of action may well be central. These same authors have shown that 15% to 30% of an oral dose is absorbed in the gastro-intestinal tract and that the drug is excreted largely unaltered in the urine. The blood levels reach a maximum in two to four hours after administration and fall rapidly over the succeeding four to six hours.

Material and Methods

Up to the present time five female and 15 male hypertensive patients, whose ages varied from 36 to 61 years, were treated with methyldopa for periods of four weeks to six months. Of the 20 patients, 16 were regarded as having primary or essential hypertension, but it must be emphasized that renal arteriography was not performed in any of them and thus a renal cause was not definitely excluded. All the patients had thickened peripheral arterial walls, fundal changes, and electrocardiographic evidence of left ventricular hypertrophy; almost all of them had clinical and radiographic evidence of left ventricular hypertrophy; and some had albuminuria (Table I). All warranted treatment with a hypotensive drug. In addition to the clinical features the initial blood-urea level is shown in Table I because it is an estimation of such prognostic importance.

All the patients were admitted to hospital and remained ambulant throughout their stay. During the first week all forms of treatment were discontinued, and the blood-pressure was recorded four-hourly standing, sitting, and lying down. The average of all readings taken over the 48 hours prior to the beginning of therapy was recorded (Table I). Investigations included chest x-ray examination, electrocardiography, intravenous pyelogram, urine examinations, blood count, erythrocyte sedimentation rate, liver-function tests, blood urea, and estimation of serum proteins, serum uric acid, serum electrolytes, and creatinine clearance.

Methyldopa was then given by mouth at 8 a.m., 12 noon, 4 p.m., and 8 p.m., starting with a dosage of 250 mg. The dose was increased every third or fourth day according to the response as judged by continued four-hourly blood-pressure recordings. Side-effects, when present, were recorded daily. Haematological and biochemical investigations were repeated at intervals of one or two weeks. When the clinical effects were regarded as satisfactory the patients were discharged home. They were followed up at fortnightly intervals, when clinical examination and casual blood-pressure readings were recorded. The haematological and biochemical investigations were repeated at monthly intervals.

Results

Hypotensive Effects

The results are summarized in Table II. Using the criteria of Dollery *et al.* (1960), the blood-pressure control of all patients except in Case 6 was good on leaving hospital. At follow-up examinations it was found that the dosage of methyldopa had to be increased in all patients except Cases 5 and 18 in order to maintain good control of the blood-pressure, indicating that tolerance to the drug had occurred. In two patients (Cases 3 and 7), despite a daily dosage of 4 g. of methyldopa, the diastolic blood-pressure was persistently above 100 mm. Hg. In Case 3, however, it was maintained at a much lower level than had hitherto been possible with combined guanethidine and mecamlamine, and the fundal changes regressed from grade III to grade II.

Again using the criteria of Dollery *et al.*, after following up our patients, the blood-pressure control was good in 16 and fair in two patients. In the remaining two the treatment was regarded as having failed. The daily dosage naturally depended on the response obtained (Table II), and it varied between 1 g. and 4 g. during follow-up observations.

TABLE I.—Summary of Findings in 20 Patients

Case No.	Sex and Age	Diagnosis	Average Initial B.P. (mm. Hg)	Left Ventricular Hypertrophy			Arterial Thickening	Blood Urea (mg./100 ml.)	Albuminuria	Fundus Grade*	Comments
				Clinically	E.C.G.	Chest X-ray					
1	M 56	M.H.	240/140	Moderate	Severe	Moderate	Present	30	Nil	IV	Dimness of vision before treatment
2	M 59	E.H.	215/130	Nil	Slight	Slight	"	20	"	II	"
3	F 44	R.H.	230/140	Moderate	Severe	Moderate	"	55	Present	III	Side-effects on guanethidine
4	M 48	E.H.	170/110	Slight	Slight	Nil	"	30	Nil	I	Angina of effort
5	M 61	"	175/125	Moderate	Severe	Slight	"	75	Present	II	Side-effects on guanethidine
6	M 56	R.H.	200/110	"	Moderate	"	"	40	Nil	II	"
7	M 46	E.H.	205/125	Slight	"	Nil	"	20	"	II	"
8	F 60	"	170/110	Severe	Severe	Severe	"	45	"	III	Rheumatic heart disease. Side-effects on guanethidine
9	F 57	"	190/115	Slight	Moderate	Moderate	"	20	"	II	Coexisting bronchiectasis
10	M 36	R.H.	185/140	Nil	Slight	Nil	"	50	Present	II	Old spondylitis treated with deep x rays
11	F 56	E.H.	210/125	Moderate	Moderate	Moderate	"	30	Nil	II	Old hemiplegia. Vitreous haemorrhage
12	M 52	"	190/135	"	"	Slight	"	36	"	II	Side-effects on guanethidine
13	M 44	"	180/115	Slight	Slight	"	"	48	"	I	"
14	M 55	"	195/120	"	"	Nil	"	46	"	II	No response to guanethidine
15	M 51	"	170/115	"	Moderate	Slight	"	30	"	II	"
16	M 55	"	190/125	Severe	Severe	Severe	"	37	"	II	No response to guanethidine
17	M 49	"	200/130	Slight	"	Moderate	"	47	"	II	" " " "
18	F 49	"	195/115	"	"	"	"	33	"	III	" " " "
19	M 37	"	170/125	Moderate	Moderate	"	"	35	"	III	" " " "
20	M 45	"	175/120	Slight	Slight	Nil	"	25	"	II	Severe headache

E.H. = Essential hypertension. R.H. = Renal hypertension. M.H. = Malignant hypertension. *Fundal appearances graded according to the system of Keith, Wagener, and Barker.

TABLE II.—Response to Treatment with Methyldopa

Case No.	Blood Pressure (mm. Hg)			Daily Dose (g.)	Weeks of Observation	Response	Fall in Diast. P. (mm. Hg)	Side-effects and Comments (All patients had transient drowsiness)
	Average Initial*	Average Final†	Follow-up					
1	240/140	120/80	125/85	4	17	Good	55	Diabetes. Papilloedema resolved
2	215/130	145/95	140/90	3	27	"	40	Dryness of mouth. Sensitive to cold
3	230/140	115/80	200/110	4	21	Fair	30	Dryness of mouth. Tolerance
4	170/110	120/95	140/90	3	20	Good	20	Dryness of mouth. Sensitive to cold. Mild hypotensive effects
5	175/125	125/80	130/90	2.5	6	"	35	Dryness of mouth
6	200/110	250/115	250/115	4	8	Poor	—	—
7	205/125	165/95	220/130	4	5	"	—	Tolerance
8	170/110	140/90	180/100	3.5	13	Fair	10	Fundus much improved
9	190/115	150/90	150/90	1	6	Good	25	Rapid response
10	185/140	150/90	150/90	1.5	6	"	50	Very rapid response
11	210/125	160/90	160/90	2	16	"	35	—
12	190/135	145/95	150/95	1.5	4	"	40	—
13	180/115	140/80	140/80	1	4	"	25	Nightmares initially. Dryness of mouth
14	195/120	140/90	145/95	3	6	"	25	Nightmares initially
15	170/115	125/90	130/90	1.5	4	"	25	Dryness of mouth
16	190/125	160/95	150/90	2.5	4	"	35	Nightmares initially
17	200/130	120/90	130/95	2.5	5	"	35	—
18	195/115	140/90	150/90	3	13	"	25	—
19	170/125	140/95	150/90	2	6	"	35	—
20	175/120	150/90	145/95	1.5	4	"	25	—

* Average four-hourly blood-pressure recordings during 48 hours prior to commencement of treatment.

† Average four-hourly blood-pressure recordings during final 48 hours in hospital.

‡ Difference between average initial diastolic pressure and follow-up diastolic pressure.

Side-effects

All the patients complained of drowsiness on the first day of treatment, and this continued for two days and recurred only if the dosage was increased. When patients were on a maintenance dose this symptom did not seem to be significant, and in fact most of them expressed a feeling of well-being and all slept well. None complained of lassitude, tiredness, or fatigue as noted by Irvine *et al.* (1962) and none became depressed. Three patients (Cases 13, 14, and 16) had nightmares on the night that therapy was started, but these did not recur. On direct questioning six patients (Cases 2, 3, 4, 5, 13, and 15) admitted to some dryness of the mouth, but this was of little consequence. An unexpected complaint in Cases 2 and 4 was of feeling generally cold, and in particular of cold hands. Only Case 4 had mild symptoms of postural hypotension. None had dyspeptic symptoms. Some of our patients on a normal ward diet without sodium restriction increased in weight during the first two weeks of treatment. This was not noticed by the patients, and was presumably due to transient fluid retention, although none developed peripheral oedema or signs of heart failure at any time.

Toxic Effects

Repeated blood counts and estimations of sedimentation rate, blood urea, serum uric acid, serum proteins, blood electrolytes, and liver-function tests showed no significant change. One patient (Case 1) who had been originally in hospital for five weeks on methyldopa therapy without symptoms or signs of diabetes was readmitted 14 weeks later in diabetic pre-coma. His blood sugar was found to be 1,000 mg./100 ml. with ketonuria. Massive insulin dosage was necessary in his emergency treatment. Subsequently the amount of insulin necessary for control became less until 14 days after admission none was required. Since then glycosuria has almost ceased and random blood-sugar estimations have been within normal limits on a normal ward diet. A glucose-tolerance test performed one week after the insulin was stopped showed a mild diabetic curve with a resting blood sugar of 100 mg./100 ml. rising to a maximum of 207 mg. and falling to 180 mg. after two and a half hours. It is possible that methyldopa in some way precipitated the onset of diabetes in this man, but the whole episode could have been fortuitous. After this experience blood-sugar estimations were performed in all the other patients in this series and were found to be normal.

Discussion

Favourable reports on the use of methyldopa as a hypotensive agent have already been published by Gillespie *et al.* (1962) and Irvine *et al.* (1962). Our observations made on 20 patients in hospital confirm that the drug was effective in 18 of them. A notable finding was the lowering of the blood-pressure in both the lying and standing positions, whereas with guanethidine and other hypotensive drugs the lying pressure is often unaffected. The blood-pressure response to methyldopa was reasonably predictable without undue fluctuations, so that the chances of precipitating a coronary or cerebral occlusion seemed small and in none of our patients did these complications occur. Only one patient developed mild symptoms of postural hypotension.

There were no toxic effects from continued use of methyldopa in this series, and the most significant and gratifying feature was the absence of disturbing side-effects. The drowsiness which has previously been noted by others (Gillespie *et al.*, 1962; Irvine *et al.*, 1962) invariably occurred in our patients but was in no way incapacitating, and in general the patients welcomed the tranquillizing effect. Similarly, other mild side-effects such as dryness of the mouth, nightmares, and increased sensitivity to cold caused no real inconvenience. Eight patients who had previously been treated with guanethidine in a single morning dose emphasized their preference for the new drug. The total daily dose of methyldopa used in some of the patients was of the order of 3 to 4 g. and many of them commented unfavourably on the excessive number of 250-mg. tablets which they were required to take at four-hourly intervals.

During follow-up observations the dose of methyldopa required for maintenance of adequate control increased in most cases, and it therefore seems probable that tolerance to its action will be a problem in the long-term use of the drug. It is obvious, however, that the period of observation in this series has been too short to permit firm conclusions on this point.

One patient with malignant hypertension (Case 1) who had a favourable initial blood-urea level of 30 mg./100 ml. was included in this trial. The response was excellent and the fundal changes, including papilloedema, regressed most satisfactorily.

From our preliminary observations we believe that methyldopa is a useful addition to the range of drugs at present in use for the treatment of hypertension, its greatest attribute being the absence of significant side-effects. In view of this and its smoothness of action, it may well prove to be the drug of choice in the initial treatment of many hypertensive patients.

Summary

Twenty hypertensive patients were treated with from 1 to 4 g. of methyldopa (aldomet) daily for periods of four weeks to six months.

It was found to be effective in most of them. There were no toxic effects from the drug. The only common side-effect was mild and transient drowsiness, and this was not incapacitating. All the patients felt better during treatment.

It is concluded from this small series of patients who have been followed up for only a relatively short time that methyldopa is a valuable hypotensive agent.

We are grateful to Dr. J. J. F. Merry, of Merck Sharp and Dohme Limited, for a generous supply of methyldopa (aldomet).

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The Society of Physicians in Wales met at the Hotel, Portmeirion, on May 11 and 12. The meeting was very well attended and seven scientific papers were given by members of the society and by a guest.