DEBRISOQUINE SULPHATE—A NEW ANTIHYPERTENSIVE AGENT WITH MINIMAL SIDE-EFFECTS

By Beatrice T. M. Chen, M.B., M.R.A.C.P.
(Senior Registrar, Medical Unit II, General Hospital, Singapore)

Methyldopa and guanethidine are the commonly used antihypertensive agents in the management of moderate to severe hypertension. In general, they are very effective drugs. However, there remains a small group of patients who either develop intolerable side-effects to these drugs, or who are unresponsive to them, singly or in combinations. It was therefore decided to conduct a trial on debrisoquine sulphate (Declinax) which has been shown to be as effective as guanethidine in the management of hypertension but with fewer side-effects (Gent and Bacon, 1967; Kitchin and Turner, 1966; Athanassiadis *et al*, 1966).

PHARMACOLOGY

Debrisoquine sulphate (3-4 dihydro-2 (1H) isoquinoline carboxamine sulphate) (Fig. 1) is a

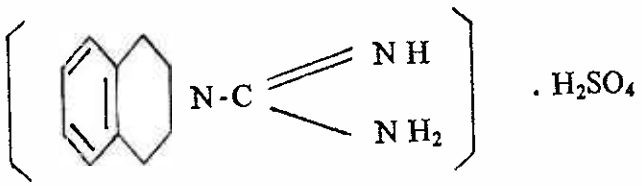

Fig. 1.

relatively new antihypertensive agent first synthesised in 1961 and has been made generally available since 1966. It blocks post-ganglionic outflow without interfering with parasympathetic activity and has therefore a similar action to that of guanethidine although chemically they are not related.

Like guanethidine, in anaesthesised dogs and in hypertensive patients, a single intravenous dose of debrisoquine sulphate will produce an initial rise of blood pressure lasting 1 to 4 hours, followed by a hypotensive effect lasting more than 4 hours. Abrams and his colleagues (1964) found no pressor effect with oral administration although Luria and Freis (1965) found that a large oral dose could produce an initial pressor effect.

After oral administration, debrisoquine sulphate is rapidly absorbed and a hypotensive effect occurs lasting 8 to 12 hours. The blood pressure fall is found to be more marked in the erect than in the supine position. Within 24 hours of ingestion, over 70 per cent of the drug is excreted in the urine, partly unchanged and partly in the form of three metabolites. From 10 to 15 per cent of the drug is excreted in the faeces. Haemodynamic studies show that there is only a small reduction of cardiac output in the supine position and a marked reduction occurs when the patient is in the erect position. Renal blood flow and glomerular filtration rate are not altered in the supine position. There is, however, marked reduction in the renal blood flow in the erect posture whereas glomerular filtration rate is not affected (Abrams *et al*, 1964; Onseti *et al*, 1966).

MATERIAL AND METHOD

Between December 1968 and October 1969, patients with diastolic blood pressure of 120 mm. Hg. or more on 2 consecutive days were given the drug. These included patients seen for the first time in Medical Unit II, General Hospital, Singapore and patients who had been under treatment in the same unit for some time but whose blood pressures were not responding to available antihypertensive agents, either singly or in various combinations. Patients with blood urea of more than 70 mg.% were not included in the trial.

All patients were admitted to the hospital when the drug was started. No drug was given for two days after admission and the blood pressure was measured in the supine and erect postures twice a day to obtain baseline readings. Routine investigations done prior to treatment were: full haematological investigations, urinalysis, blood urea, serum uric acid, serum electrolyte, creatinine clearance and intravenous pyelogram. Haematological investigations and creatinine clearance were repeated at the end of 6 months of therapy. The blood pressure was measured in the supine and erect postures twice daily and body weight was recorded before breakfast. Side-effects were asked every day and recorded when present.

The initial dose of debrisoquine sulphate was 10 mg. twice a day. This was increased by 5 mg. increment per dose every 2-3 days. When the blood pressure was relatively well controlled, the patients were discharged to be followed up as out-patients, weekly at first for one month and

subsequently fortnightly or monthly. Chlorothiazide 0·5 gm. daily was given if the patient showed progressive increase in body weight and his blood pressure not controlled.

The aim of treatment was to reduce the blood pressure to as normal a level as possible without side-effects. The criteria of response was based on that of Dollery *et al* (1962). A sustained fall of diastolic pressure to 100 mm. Hg. or less either in the lying or standing position was regarded as good response; a fall of diastolic pressure of 20 mm. Hg. or more but above 100 mm. Hg. as fair. Responses of less than 20 mm. Hg. in diastolic pressure were considered to be poor.

RESULTS

Between December 1968 and October 1969, 22 patients with a diastolic blood pressure of 120 mm. Hg. or more on two consecutive days were started on debrisoquine sulphate. They included 13 patients with hypertension seen for the first time and 9 patients who failed to respond to available antihypertensive therapy for a period from 4 months to 5 years.

Two of the 13 new cases died at 2 weeks and 3 months after starting treatment because of acute myocardial infarction and cerebral haemorrhage respectively. They were not included this series because of inadequate follow-up, and in the case of the second patient, irregularity in taking his medicine.

Altogether 20 patients were treated with debrisoquine sulphate for a period of 4 months to one year (Table I). Table II gives a summary of clinical data of these 20 patients.

The 9 old cases had been followed in our out-patient clinic for a period ranging from 4 months to 5 years (average 25·5 months). Their blood pressure were not controlled with the available antihypertensive agents in maximal doses using reserpine, guanethidine, methyldopa and mecamylamine (Table III), and diuretics such as chlorothiazide, frusemide and clorexolone.

The initial controlling dose ranged from 20 mg. to 70 mg. per day in two divided doses, with an average of 46·25 mg. per day (Table IV). Twelve patients obtained good control of blood pressure, 4 had fair control and 4 failed to respond. Of the 4 patients who did not respond, 3 were old cases in whom the dose of debrisoquine sulphate were increased to more than 200 mg. per day before they were taken off the drug. The remaining one patient, a new case, failed to respond at a dose of 100 mg. per day and therapy was changed at this stage because he developed severe diarrhoea. Of the 16 patients with Grade II retinopathy, 10

TABLE I

DURATION OF THERAPY IN 20 PATIENTS

4 months	1
6 months	3
7 months	2
8 months	2
9 months	2
10 months	2
11 months	4
12 months	5

Average follow-up period 9·55 months

TABLE II

CLINICAL DATA OF 20 PATIENTS

New cases	11
Old cases	9
Sex:	
Male	9
Female	11
Age:	
30 - 39	3
40 - 49	7
50 - 59	6
Over 60	4
Race:	
Chinese	15
Malay	3
Indian	2
Diagnosis:	
Essential hypertension	13
Chronic glomerulonephritis	6
Chronic pyelonephritis	1
Fundal Grading:	
Grade I	0
Grade II	16
Grade III	1
Grade IV	3

TABLE III

PREVIOUS ANTIHYPERTENSIVE THERAPY

Drug	No. of Patients
Guanethidine	9
Methyldopa	9
Reserpine	4
Mecamylamine	1

TABLE IV

DOSE OF DEBRISOQUINE SULPHATE FOR INITIAL CONTROL

(mg. per day)

20	- - 2	50	- - 3
30	- - 1	60	- - 3
40	- - 5	70	- - 2

Mean: 46·25 mg. per day

responded well, 3 fairly well and 3 did not respond. The one patient with a Grade III retinopathy obtained good response. Of the 3 patients with malignant hypertension, the response was equally distributed in each category (Table V).

TABLE V

FUNDAL GRADING AND INITIAL RESPONSE

	II	III	IV
Good response	10	1	1
Fair response	3	0	1
Poor response	3	0	1

The time taken to obtain control of blood pressure in the 16 patients ranged from one week to 4 months (Table VI). As the trial progressed, it was found that some patients required an increase in dose to maintain a response.

TABLE VI

TIME FOR CONTROL OF BLOOD PRESSURE

1 week - - - -	6
2 weeks - - - -	1
3 weeks - - - -	1
4 weeks - - - -	3
5 weeks - - - -	1
6 weeks - - - -	1
3 months - - -	2
4 months - - -	1

Mean: 3·3 weeks

Side-effects were minimal and seldom disabling (Table VII). Nine patients showed progressive increase in weight due to fluid retention and had to be given chlorothiazide. Eight patients had postural hypotension but only 2 complained of giddiness relating to posture. Only 2 patients complained of stuffy nose and one of them also complained of weakness and lethargy. This latter patient did not respond to treatment at all. Two patients developed diarrhoea; in one of them it was severe enough to warrant withdrawal of the drug. The other patient had mild diarrhoea only; in addition he also complained of feeling cold while on the drug. He, too, did not respond to the drug at a dose of 220 mg. per day. Five patients had no side-effects at all.

TABLE VII

SIDE-EFFECTS TO DEBRISOQUINE SULPHATE

Fluid retention - - - -	9
Postural hypotension - - -	8
Blocked nose - - - -	2
Diarrhoea - - - -	2
Lethargy - - - -	1
Weakness - - - -	1
Feeling cold - - - -	1
No side-effects - - - -	5

At the end of 6 months, none of the 19 patients developed any haematological disorders, including autoimmune haemolytic anaemia such as which occurs in some patients on methyldopa. There was also no appreciable changes in creatinine clearance in these patients at the end of 6 month therapy.

DISCUSSION

Debrisoquine sulphate is a sympathetic blocking agent similar in action but different in structure to that of guanethidine. The onset of action is, however, rapid and it is therefore quicker to achieve control of blood pressure with this drug than with guanethidine. An optimal initial response can be obtained within one week although some cases may take as long as 4 months. Like guanethidine, the controlling dose varies widely—between 20 and 70 mg. per day with an average of 46·25 mg. in this series. Other authors have reported a wider range (10 to 120 mg. per day with an average of 45 mg.; Kitchin and Turner, 1966).

The greatest advantage of this drug over the available antihypertensive agents such as methyldopa and guanethidine is the notably fewer and less severe side-effects. Of the 20 patients in this series, 5 were completely free from any side-effects. One of them was particularly pleased with the drug because it did not cause impotence and failure to ejaculate, a side-effect which he had experienced with other antihypertensive agents. Nine patients had to be given chlorothiazide because of steady weight gain during each visit; in one of them fluid retention was so severe that

he exhibited signs of early heart failure which required digitalisation. The only other series in which fluid retention causing signs of early heart failure was recorded was that of Athanassiadis *et al* (1966), and fluid retention was not a major complication in the series of 45 patients reported by Kitchin and Turner (1966). Unlike other reports (Gent and Bacon, 1967), there was no necessity to reduce the dose of debrisoquine sulphate when a diuretic was added to the regime of treatment. As with other series, postural hypotension is one of the commonest side-effects. In addition, exertional dizziness has been recorded in cases no exhibiting postural hypotension (Gent and Bacon, 1967; Athanassiadis *et al*, 1966); this was not present in the present series. None of our patients complained of exertional muscle pain, blurred vision or nocturia (Athanassiadis *et al*, 1966; Kitchin and Turner, 1966). Diarrhoea was said to be severe in 4 out of 7 patients described by Athanassiadis *et al* (1966) but Kitchin and Turner (1966) reported only 2 patients with mild diarrhoea. In this series, 2 patients had diarrhoea and in only one of them was this severe enough to warrant withdrawal of the drug. However, both of these patients did not achieve good control of blood pressure, even though in one of them the dose of debrisoquine sulphate was pushed up to 220 mg. per day. The patient who had mild diarrhoea also complained of feeling cold, a side-effect which has not been reported in the literature reviewed. None of the 20 patients developed any haematological disorders including autoimmune haemolytic anaemia, had depression or showed appreciable deterioration of glomerular filtration rate at the end of 6 months of treatment. This is in agreement with all reports reviewed.

Like guanethidine, some degree of tolerance to debrisoquine sulphate developed, i.e., an increase in doses over that achieved for initial controlled was required in some patients as the trial progressed. This is in accordance with the findings of Kitchin and Turner (1966) and Athanassiadis *et al* (1966) but at variance with the report of Gent and Bacon (1967).

Of the 9 cases who did not respond to available antihypertensive agents in various combinations and diuretics, 5 patients obtained good response and one a fair response. The remaining 3 did not respond. Athanassiadis *et al* (1966) also reported response to debrisoquine sulphate in patients who failed to respond to methyldopa and guanethidine.

Debrisoquine sulphate is therefore an effective antihypertensive agent with the added advantage of having remarkably few side-effects. It was also found to be effective in cases not responsive to other antihypertensive agents. Although in some centres (Gent and Bacon, 1967), it is considered the agent of choice in the management of hypertension, it is the author's opinion that this drug should be regarded only as an useful addition and alternative to the array of antihypertensive agents available. For as with all conditions for which more than one drug is available for management, it is better for the physician to be familiar with one drug and to change only when this drug fails to achieve the desired result.

SUMMARY

Twenty patients were given debrisoquine sulphate (Declinax) for a period of 4 months to one year. Good control was obtained in 16 patients, fair control in 4 and poor control in 4. Six of the 9 patients who had not responded previously to other antihypertensive agents responded to debrisoquine sulphate.

The drug is as effective as guanethidine and methyldopa in the management of moderate to severe hypertension. It has, however, the distinct advantage over the latter in producing remarkably few side-effects.

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