caused by bacterial strains whose patterns of resistance exclude the usual primary agents—sulphanilamide, nitrofurantoin, and penicillins.

Summary

The excretion of biologically active chloramphenicol in urine diminishes linearly with decreasing renal function. When the renal function is reduced to an endogenous creatine clearance under 20 ml./min., less than 1% of the dose administered is excreted as the active compound, compared with 5–10% for normal renal function. The maximum excretion of chloramphenicol found at this degree of renal insufficiency was 10–20 µg./ml. of urine, compared with 150–200 µg./ml. for normal renal function.

The low concentrations of urine might explain the poor correlation between chloramphenicol sensitivity tests *in vitro* and the results when treating infections of the urinary tract in patients with renal insufficiency. In elderly patients with a physiologically decreased renal filtration the urinary concentrations of chloramphenicol might be too low, increasing the risk for development of drug-resistant micro-organisms.

The level of biologically active chloramphenicol in blood was only slightly influenced by the renal function, while metabolites of the drug accumulated in patients with decreased renal function.

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Studies on Debrisoquine Sulphate

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Control of the blood-pressure in hypertensive patients is now easier with drugs in current use. In the majority of patients blood-pressure can be reduced considerably, and usually, but not always, maintained at the desired level without undue side-effects or intermittent hypotension. Consequently, with adequate drugs already available it is becoming more difficult to assess the relative merits of new preparations.

It takes at least 12 months to form a preliminary assessment of a promising new drug, and the first patients have usually been under treatment for two to three years before a confident opinion can be given on an adequate number of cases, particularly as regards tolerance.

In this country ganglion-blocking agents have been largely superseded by preparations which have no effect on the parasympathetic nervous system. At the present time most patients with severe hypertensive disease are probably being treated with the sympathetic-blocking drugs guanethidine or methyl-dopa, but clinical trials on new preparations are going on in many hospitals.

Patients vary in their preferences for different drugs largely owing to the varying side-effects.

Rather than carry out comparative trials or double-blind trials with different preparations in the same group, it is now sufficient to try different preparations only in those who cannot tolerate the drug with which most experience has been gained.

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With regard to the assessment of new preparations, hospitals with facilities for clinical research can usually tell from a pilot trial on an adequate number of patients whether a new preparation is likely to prove an advance and whether trials on a larger scale are warranted.

In our experience guanethidine was a distinct advance over previous preparations, but, nevertheless, tolerance in a few patients and side-effects in many necessitated the giving of adjuvants or antidotes in about half the cases. Only 60% of patients treated for more than two years maintained a good or fair result. It was concluded that, although guanethidine, particularly in combination with an oral diuretic, was better than previously available drugs for the long-term treatment of hypertension, it had a number of disadvantages (Lowther and Turner, 1963).

Methyldopa proved to be equally effective as regards reduction of blood-pressure. On the whole, side-effects were fewer and less unpleasant, but some patients were completely intolerant of side-effects; others felt generally unwell, and most experienced unpleasant symptoms in some degree (Johnson, Kitchin, Lowther and Turner, 1966).

Some patients therefore preferred methyldopa and others guanethidine, but neither preparation was entirely satisfactory. Consequently we agreed to carry out a pilot trial with a new and more promising drug with an action reputed to be similar to that of guanethidine.

Debrisoquine sulphate (Declinax) was originally synthesized in 1961, and is a colourless, crystalline, water-soluble substance.

Pharmacology and Metabolism

The cardiovascular effects in animals have been described by Moe, Bates, Palkoski, and Banziger (1964). In many respects the mode of action resembles that of both bretylium and guanethidine in that post-ganglionic sympathetic activity is blocked, but, unlike guanethidine, peripheral stores of noradrenaline are not depleted. However, unlike bretylium, which is a noradrenaline depleter, debrisoquine does not alter the uptake nor release of exogenous noradrenaline in studies of rats' hearts *in vivo* with tritiated material.

In man, Pocelinko and Abrams (1964) have confirmed the animal work showing that intravenous administration of debrisoquine produces a marked pressor phase which lasts approximately two to three hours, followed by a depressor phase lasting up to eight hours. After the oral administration of this compound no pressor phase occurs. The hypotensive effect of a single oral dose occurs within four hours and lasts from 9 to 24 hours; this effect is more pronounced in the upright position. The clinical onset of action is therefore short and is not followed by prolonged hypotension as with guanethidine. After treatment with debrisoquine in humans, exaggerated responses to the noradrenaline and tyramine tests occur, which is in contradistinction to the effects produced by guanethidine. Preliminary haemodynamic and renal-function studies suggest that the hypotensive effects of debrisoquine are associated with diminished peripheral vascular resistance, a relatively good preservation of cardiac output and well-maintained renal flow, but diminished glomerular filtration in the erect position.

The metabolism of debrisoquine has been studied by the Roche Clinical Research Department, material labelled with ^{14}C in the amidine carbon position being used. After intraperitoneal administration to rats the highest concentrations were found in liver, heart, kidneys, and lungs. Lower levels were found in these tissues after oral administration. Fifty-two per cent of the dose was excreted in the urine and 42% in the faeces after intraperitoneal dosing, whereas after oral administration 37% of the dose was excreted in the urine and 50% in the faeces. The fall-off in the rate of urinary excretion in the rat was characterized by a half-life of eight hours after intraperitoneal doses and seven hours after oral administration.

In two human subjects oral doses of 50 mg. of labelled material showed that 73% of this dose was excreted in the urine. This was mainly present in the form of metabolites. The total excretion of radioactivity in both subjects in eight days was 80% in the urine and 12% in the faeces. No labelled pulmonary carbon dioxide was detectable. After four hours of administration only 30% of the blood ^{14}C material of each subject was estimable. The metabolism of debrisoquine therefore appeared to be rapid in these subjects.

In the dog the pattern of excretion was similar to that in man, a total of 90% of the dose being excreted in the urine and 10% in the faeces. Chromatography of human urine showed the presence of unchanged debrisoquine and also three metabolites. The dog urine contained a further metabolite. Although the metabolites were not identified, it was shown that they were basic in nature and that all contained an intact guanidine moiety.

Clinical Trial of Debrisoquine

Patients and Methods

Forty-five patients were treated with debrisoquine for periods ranging from 12 to 34 months (Table I). In addition 10 patients stopped treatment earlier than this for reasons discussed later.

Ages ranged from 30 to 66 years, with a mean of 52. Of the 55 patients, 22 were male and 33 female. Table II includes the age distribution related to the severity of the disease. Indications for treatment, selection of patients, measurements of blood-pressure, and classification of results were similar to those we have previously described in relation to other drugs. Therefore patients entered in the trial were only those who, in addition to high resting diastolic pressures, showed objective

evidence of secondary changes in the retina, the heart, and sometimes the kidneys. Table II summarizes the clinical features of the 55 patients, who represent a fair cross-section of those with severe hypertensive disease.

TABLE II.—*Clinical Features*

		Severe Hyper- tension	Moderate Hyper- tension	Total
Patients' age groups	30-40	5	3	8
	41-50	6	5	11
	51-60	16	10	26
	61-70	9	1	10
Mode of presentation	Left ventricular failure ..	9	1	10
	Cerebrovascular accident ..	8	1	9
	Headache	10	8	18
	Visual disturbance	3	0	3
	Routine examination	4	3	7
Renal function	Miscellaneous	5	3	8
	Normal	30	15	45
E.C.G. changes	Impaired	9	1	10
	L.V. hypertrophy (present) ..	33	2	35
	L.V. " (absent)	6	14	20
Retinal changes	Normal	0	1	1
	Grade I	4	6	10
	" II	8	8	16
	" III	25	0	25
	" IV	3	0	3
Resting diastolic pressure before treatment	105-129	11	7	18
	130-149	21	8	29
	150+	8	0	8

Retinal changes were classified for convenience according to the criteria of Keith, Wagener, and Barker (1939), although this classification has disadvantages, as previously discussed (Turner, 1959; Stokoe and Turner, 1966). Criteria for the electrocardiographic diagnosis of left ventricular hypertrophy were those recommended by Sokolow and Lyon (1949) modified according to the recommendations of Simonson (1961). Impaired renal function denoted abnormal values of endogenous creatinine clearances or phenolsulphonphthalein excretion, but with blood-urea level within normal limits.

Recording of Blood-pressure.—Blood-pressure was recorded by trained technicians, the reading being taken after the fourth successive inflation of the sphygmomanometer. Each reading represents the mean of several measurements taken at intervals. Pressures were recorded in the lying position and again after the patient had been standing for two minutes. In most cases they were repeated after exercise on at least one occasion and whenever there was doubt whether the drug was working. The "resting" pressures used as baselines for assessment of the results were recorded in the above manner after the patient had been resting in the ward for a few days during the period of preliminary investigation. In patients who were not first admitted to the ward the initial blood-pressure was taken as the average of those recorded after their confidence had been gained.

Drug Regimen.—The initial dose of debrisoquine was usually 10 mg. given twice daily. Increments were then added every third day, depending on response, in those patients whose treatment was initiated in hospital and at weekly intervals in outpatients until an adequate response was obtained. In most patients throughout the early part of the trial debrisoquine was used alone; oral diuretics were used at this stage only for the treatment of fluid retention or in patients who had previously been on some other drug, together with a diuretic.

The daily dose in the initial stages of treatment ranged from 10 to 120 mg., with an average of 45 mg. Later on the average daily dose ranged from 20 to 200 mg., with an average of 74 mg. As the trial progressed it became obvious that more patients required an increase in debrisoquine over the initial responsive dose, and also that an increased number of patients required the addition of a thiazide diuretic.

Aims of Treatment.—The usual aim of treatment, as in our previous studies on antihypertensive drugs, was to reduce the

TABLE I.—*Duration of Follow-up in 45 Patients*

12-18 months in 18 cases	25-30 months in 14 cases
19-24 " " 11 "	31-34 " " 2 "
Average period of follow-up, 22.1 months.	

standing diastolic pressure to as near normal levels as could be achieved without undue side-effects. Only the fall in pressure achieved and maintained has been considered in classifying the result of the treatment. In patients with symptoms or signs suggestive of cerebral or coronary atherosclerosis or with evidence of impaired renal function, the aim was to achieve only moderate control over the blood-pressure, and, in particular, to avoid undue postural falls in pressure. A "good" result signifies a reduction in blood-pressure of 30/20 mm. Hg, and a fall in diastolic pressure below 100 mm. Hg. A "fair" result signifies a fall of 30/20 mm. Hg with a diastolic pressure between 100 and 110 mm. Hg. A "poor" result denotes failure to achieve a significant fall in pressure.

Results

Of the 55 patients¹ originally entered in the trial 10 either died or stopped treatment, and these are described in more detail below. Of the remaining 45 patients (20 males and 25 females) 31 were classified as having severe hypertension and 14 as having moderate hypertension. Twenty-two had previously received other antihypertensive drugs and 23 had had no previous treatment for their hypertension.

In the majority of patients initial control over the blood-pressure—for example, after three to four weeks—was achieved satisfactorily; most patients at that stage were being treated without the aid of diuretics in order to assess the efficacy of debrisoquine alone compared with drugs in previous use. Continued follow-up, however, showed that in many patients the dose had to be raised considerably in order to maintain an adequate response, and about 18 months after the start of the trial it was decided that the addition of a diuretic would be advisable in those on the higher dose range. Table III summarizes the results obtained at the initial control phase and again at 6, 12, 18, 24, and 30 months. It will be seen that during the earlier phase of the trial the percentage of good results diminished but later on improved again owing to the increased use of an *additional* diuretic.

TABLE III.—Results

	Control	Patients		Total	%
		Moderate	Severe		
Initial	Good	6	24	30	67
	Fair	4	3	7	15
	Poor	4	4	8	18
At 6 months	Good	9	10	19	42
	Fair	3	11	14	31
	Poor	2	10	12	27
At 12 months	Good	9	14	23	51
	Fair	4	10	14	31
	Poor	1	7	8	18
At 18 months	Good	6	10	16	52
	Fair	3	5	8	26
	Poor	1	6	7	22
At 24 months	Good	3	12	15	60
	Fair	3	5	8	32
	Poor	1	1	2	8
At 30 months	Good	2	5	7	64
	Fair	0	3	3	27
	Poor	0	1	1	9

The following is a brief summary of each of the 10 patients who did not complete the trial:

Case 4.—A woman aged 53 developed nausea, diarrhoea, and exhaustion while on debrisoquine and treatment had to be stopped. Previously she had complained of similar symptoms on other drugs and was thought to have a low threshold for symptoms.

Case 6.—A woman aged 57 initially had a good response to debrisoquine and a thiazide but developed congestive failure from cor pulmonale, and it was thought that her hypertension was relatively unimportant and did not warrant further treatment in the circumstances.

¹ Details of these cases can be obtained from Dr. R. W. D. Turner, 12 George Square, Edinburgh 8.

Case 15.—A woman aged 53 had a satisfactory initial response but throughout the first year developed tolerance despite the addition of a thiazide, and died from a stroke one week after stopping treatment on her own accord. She had had no side-effects, and it was not thought that her death was attributable to debrisoquine.

Case 25.—A woman aged 63 died from myocardial infarction after four months' treatment, but it had previously been thought that ischaemic heart disease was more important than hypertension in her case. She was on a small dose of the drug and had experienced mild postural dizziness but not syncope.

Case 30.—A man aged 49 maintained a moderate response on a dose of 50 mg. of debrisoquine for nine months but then left the district.

Case 32.—A man aged 64, after an initial good response to 40 mg. of the drug, developed tolerance throughout the following year, being poorly controlled on a dose of 120 mg. a day. At this stage he developed angina and suffered a small stroke, and atherosclerosis was thought to be more important than hypertension.

Case 36.—A woman aged 61 had a good response to 30 mg. of debrisoquine, but after six months developed postural symptoms, following influenza. In view of this treatment was changed to another preparation but could probably have continued.

Case 37.—A woman aged 61 maintained only a fair control throughout one year's treatment. She had previously experienced a cerebrovascular accident and was constantly troubled with dizziness and ataxia. Treatment was stopped on this account.

Case 38.—A woman aged 42 initially responded well on a combination of debrisoquine and methyldopa although troubled with dizziness on exertion. After three months the response was graded as poor despite the addition of a thiazide, and tolerance persisted, with complaints of tiredness and lack of energy.

Case 43.—A woman aged 64 developed tolerance over a six-months period and then moved to another district.

Side-effects.—Fourteen patients complained of dizziness, not always associated with changes in posture, and usually corrected by a minor adjustment of dosage. Treatment did not have to be stopped on this account in any case. Three patients complained of mild nocturia, which passed off with continued use of the drug. Two patients complained of mild diarrhoea during the initial few weeks of treatment, but this passed off and did not have the embarrassing explosive quality often associated with guanethidine. A few patients complained of feeling tired. None had depression.

Tolerance.—A considerable number of patients developed some degree of tolerance, which signifies that, having initially attained satisfactory control, the blood-pressure rose again and the dose of the antihypertensive drug had to be increased or an oral diuretic added. Taking into account the percentage increase in dose or the need for adding a diuretic and the time taken to regain and maintain control, tolerance has been arbitrarily graded as mild, moderate, or severe (Table IV). Tolerance is also reflected in the average dose of debrisoquine which had to be given at different times (Table V).

TABLE IV.—Tolerance (45 Cases)

Severity	No. of Cases	%
Mild	14	31
Moderate	5	11
Severe	5	11
Total	24	53

TABLE V

Time	Average Daily Dose (mg.)		
	All Patients	Patients on Debrisoquine Alone	Patients on Debrisoquine + Diuretic
Initial control ..	45	47	40
At 6 months ..	58	57	63
" 12 " ..	69	64	77
" 18 " ..	74	78	72
" 24 " ..	77	78	74
" 30 " ..	53	57	52

Discussion

The results demonstrate that debrisoquine is an effective antihypertensive compound. The fall in blood-pressure is fairly rapid and predictable, and it is possible to establish adequate control quite quickly. Continued treatment requires careful readjustment of dosage and often the addition of an oral diuretic. The more frequently a patient can be seen the more rapidly can control be obtained, but, as with all antihypertensive drugs, caution is required against hypotension, and if an oral diuretic is added the dose of the principal agent being used should at the same time be reduced in the first instance.

Side-effects are notably less frequent, less severe, and less unpleasant than with any other effective preparation previously used for lowering blood-pressure, and, in particular, in comparison with guanethidine or methyldopa, which are probably the two sympathetic-blocking agents principally used in this country at the present time. There can be no doubt that all patients previously treated with other drugs much preferred debrisoquine on this account.

It is not to be expected that all patients with hypertension, especially those with secondary changes in the cardiovascular system, will be entirely free from side-effects if the blood-pressure is lowered by the mechanism of sympathetic blockade. The autonomic nervous system is widespread and interference must produce some degree of unwanted effects. Minor differences in the pharmacology of guanethidine and debrisoquine may account for some of the diminished side-effects of the latter. These may be attributable to the fact that debrisoquine does not deplete the peripheral stores of nor-adrenaline.

We have not seen serious toxic effects occurring with this compound over long-term use. The deaths in this series were attributable to the natural history of the disease process rather than to the direct effect of the drug. No perfect antihypertensive agent has yet been devised, and one must judge any advantages of one over the other on the score of effective therapeutic response in relation to the incidence of side-effects. Debrisoquine has shown distinct advantages over some of the other antihypertensive drugs used, and may prove to be a significant advance.

What is meant by "tolerance" is a matter of definition. Strictly speaking, once the blood-pressure has been reduced and maintained at the required level for a few weeks or months, any subsequent increase in dosage that is necessary to keep it there may be termed "tolerance."

It is usual with any antihypertensive drug for small increases in dosage to be required during the initial stages of treatment and also at the first outpatient attendance after discharge from the hospital ward and a return to a normal domestic and working environment. Such initial increases in dosage are unimportant. Important tolerance implies that once having gained satisfactory control over the blood-pressure a repeated increase in the dose is required to maintain such control, if indeed control can be maintained at all. Sometimes in such cases tolerance can be overcome by the addition of an oral diuretic or combination with some other antihypertensive drug.

It might be argued that if control can be maintained by steadily increasing the dose at each visit, or by the addition of an oral diuretic, then this is of no particular consequence. However, tolerance in this degree necessitates relatively frequent visits to the clinic, a requirement which is tiresome for the patient and often a considerable strain on the hospital resources. Also it implies that the blood-pressure has not been adequately controlled.

It was our experience with guanethidine and also with methyldopa that successive increases in dosage in the early weeks of treatment usually led to an exacerbation of side-effects, but the relative absence of important side-effects with debrisoquine is a very definite advantage in this respect.

An answer to tolerance might be obtained more rapidly if patients were asked to attend the clinic at shorter intervals or if an oral diuretic had also been given from the beginning. However, it seems reasonable first to assess a new drug on its own merits. If the pressure is reasonably well controlled and the patients are sufficiently well to continue work or normal household activities we are reluctant to ask them to attend more often for the sake of a clinical trial, but only if they have experienced side-effects or if tolerance is severe enough in degree to make frequent visits essential to maintain control over the blood-pressure.

It would of course be possible to carry out a trial by omitting the oral diuretic after control of the blood-pressure had been obtained, but this would mean to run the risk of a sudden rise in pressure and consequently of a cerebrovascular accident.

In some cases adjustments in dosage can be made by the practitioner to save the patient extra visits to the clinic.

In these circumstances final determination of the relative importance of the development of tolerance to the successful use of this drug must await further experience, but it is not a sufficient disadvantage to discourage its use.

It is concluded that debrisoquine is an effective antihypertensive agent which is remarkably free from side-effects, and although an oral diuretic may have to be given in addition to many patients this also applies to all other antihypertensive drugs of which we have experience.

Summary

The results are presented of the treatment of 55 patients with severe hypertension for 12 to 34 months with a new antihypertensive drug, debrisoquine (Declinax).

This compound has proved to be an effective antihypertensive agent remarkably free from side-effects, and in this regard a distinct advance over guanethidine or methyldopa.

The only disadvantage encountered so far has been a higher incidence of tolerance than is experienced with other drugs in current use, necessitating the administration of an oral diuretic in many cases.

In view of its favourable properties we consider that debrisoquine should be subjected to wider clinical trial.

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