DESCRIPTION OF SPECIAL PLATE

FIG. 1.—Tomogram of kidneys. The double-line pattern of cortical calcification can be clearly seen. By inspection of tomographic cuts at other levels it was possible to trace the double-line pattern around most of the cortex. The double-line pattern was visible in the plain x-ray film, but was not dense enough to allow satisfactory reproduction.

FIG. 2.—Post-mortem radiograph of kidneys showing double-line pattern of calcification, which can be traced around almost the entire cortex. There is calcification of the thrombus in the ovarian veins.

FIG. 3.—Section through kidney showing extensive cortical necrosis.

FIG. 4.—Two bands of dense calcification are shown. Both the subcapsular tissue distal to the outer band and the medullary tissue proximal to the inner band contain renal elements which escaped the ischaemic process. Virtually all tissue between the two bands is necrotic. ($\times 4.5$.)

FIG. 5.—Necrotic renal cortex showing calcification in glomerular tuft and dilatation of a necrotic interlobular artery. ($\times 100$.)

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Canada now has 21,000 active doctors, according to the 1962 edition of the *Canadian Medical Directory*. Another 1,300 doctors are retired or overseas. The *Directory* reports that the ratio of doctors to population has been rising steadily. To-day there is one active doctor for every 868 Canadians. Five years ago, in 1957, there was only one active doctor to every 970. The province with the best ratio this year is British Columbia, where there is one active doctor for every 826 people. The lowest ratio is found in Newfoundland with one doctor to every 1,960. There is a gradual trend towards more specialization in Canada. According to the *Canadian Medical Directory* only 30% of Canada's doctors were full-time specialists 10 years ago. This year 38% are full-time specialists. (Publishers, Secombe House, 443 Mount Pleasant Road, Toronto, Canada. Price \$12.)

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BRETYLIUM TOSYLATE IN TREATMENT OF SEVERE HYPERTENSION

BY

K. SOMERS, M.B., B.Ch., M.R.C.P., D.C.H.

Senior Lecturer in Medicine, Makerere University College Medical School, Kampala, Uganda

(From the Department of Medicine, Makerere University College Medical School, and the Medical Division, Mulago Hospital, Kampala, Uganda)

Ganglion-blocking drugs provide the most effective means of controlling severe hypertension. Their usefulness may be limited in some patients by the occurrence of the disabling side-effects of parasympathetic blockade. A drug that would block sympathetic activity without affecting parasympathetic function might be expected to show the hypotensive action of the ganglion-blocking agents without the unpleasant side-effects. Bretylium tosylate has such properties. Introduced by Boura *et al.* (1959), bretylium tosylate blocks the sympathetic nervous system by its selective accumulation in sympathetic ganglia and post-ganglionic sympathetic fibres.

Following on encouraging reports of clinical trials (Boura *et al.*, 1959; Dollery *et al.*, 1960a) there has been a considerable correspondence (Turner and Lowther, 1960a, 1960b; Evanson and Sears, 1960; Lowe and Rosenheim, 1960; Somers, 1960a) recording unfavourable experiences with bretylium. Ultimately Dollery *et al.* (1960b) abandoned the use of bretylium because of the high incidence of drug resistance.

The findings reported in this paper refer to experiences with bretylium at an African hypertension clinic, the organization of which has been described elsewhere (Somers, 1960b).

Clinical Observations

Patients were admitted to hospital for initial assessment. After discharge they were followed up at a special clinic. A total of 29 patients (11 males, 18 females) were treated with bretylium tosylate. Their age distribution is shown in Table I. As previously reported from this clinic (Somers, 1959, 1960b, 1961), over half of the patients have chronic renal hypertension. This contrasts with experience in Western countries,

TABLE I.—Age of Patients

Age	20-30	31-40	41-50	Over 50
No. of patients	6	6	10	7

TABLE II.—Clinical Findings in 29 Patients Treated with Bretylium Tosylate

Diagnosis	No. of Patients	No. with Renal Failure
Essential hypertension	15	1
Renal hypertension :		
Chronic glomerulonephritis ..	3	1
Chronic pyelonephritis ..	10	3
Toxaemia of pregnancy ..	1	0
Total	29	5

where essential hypertension is the more common. In the series, essential and renal hypertension were equally represented (Table II). Five patients showed evidence of chronic renal failure—that is, had blood-urea levels persistently in excess of 60 mg./100 ml. No patient with blood-urea levels persistently in excess of 150 mg./

100 ml. was offered treatment as it was felt that hypotensive therapy was unlikely to improve the prognosis. Most of the patients presented in left ventricular or congestive heart failure. Other indications for treatment were hypertension with changes of grade 2 or over in the fundi. Two patients had malignant hypertension. No patient with asymptomatic hypertension was given treatment. A number of patients had previously been treated with the ganglion-blocking agents pempidine or mecamlamine.

The initial dose of bretylium was 200 mg. three times daily. Gradual increases of 200 mg. and more per dose were made in attempts to produce a satisfactory fall in blood-pressure. The final maintenance dose ranged from 600 to 3,600 mg. daily. Patients were observed under treatment for periods ranging from six weeks to eight months.

Response to Treatment

The fall in blood-pressure alone was the criterion of response. This was satisfactory when a standing blood-pressure of 160/100 mm. Hg or less was observed on most occasions. Treatment was regarded as unsatisfactory if the fall in blood-pressure was not sustained or if there was no fall. A decision on the effectiveness or failure of treatment with bretylium was made when a daily dose of 3,600 mg. was reached. When tolerance to bretylium was apparent the effect of the addition of thiazide agent (chlorothiazide, hydrochlorothiazide, hydroflumethiazide, or bendrofluazide) was assessed before a final decision on response was taken. In patients with considerable resistance there seemed little point in persisting beyond 3,600 mg. a day. Supplies of the drug were being exhausted quickly and effects of uncontrolled hypertension in the sensitive patients were becoming evident. We did, however, try bretylium tosylate up to a dose of 18.6 g. a day in a patient who was extremely resistant to bretylium (Somers, 1960a).

The response was satisfactory in 14 patients and unsatisfactory in 15. An initial satisfactory response was followed by increasing resistance, which forced us to abandon further treatment with bretylium. A longer follow-up in the 14 with satisfactory response has since revealed a number of patients in whom bretylium has become less effective.

Side-effects

Side-effects were recorded only in those who volunteered information. Muscular weakness occurred in eight patients, dizziness in six, and nasal stuffiness, diarrhoea, and vomiting in one each. They were generally mild and caused no particular disablement. Relief from the side-effects of ganglion-blockade was much appreciated by all patients transferred from ganglion-blocking agents to bretylium.

Muscular weakness did not appear to be associated with the development of hypotension, and in fact often occurred in patients on high dosage. From available evidence (Campbell and Montuschi, 1960; Vernikos-Danellis and Zaimis, 1960) it seems that bretylium produces muscle weakness by direct action on muscle cell function.

Dizziness was not necessarily related to postural hypotension. Dizziness occurring after exertion in patients on bretylium has been noted by Lowe and Rosenheim (1960). In a number of our patients dizziness occurred at rest or when they were doing nothing in particular.

Illustrative Cases

The following cases illustrate some of the problems that arose in treatment with bretylium.

Case 1

A Ganda male peasant cultivator aged 50 was known to have had essential hypertension with congestive heart failure for three years. At first assessment B.P. was 210/145 mm. Hg. X-ray film showed left ventricular enlargement. E.C.G.: gross left ventricular hypertrophy. Blood urea 24 mg./100 ml. Treatment with mecamlamine 50 mg. daily had been abandoned on account of severe mecamlamine tremors. Later he was successfully stabilized on pempidine 60 mg. daily but with abdominal distension as a major side-effect. Standing B.P. was 170/100 on most occasions. He was transferred to bretylium tosylate with an initial dose of 600 mg. daily, but moderate resistance was evident from the outset. The dose was increased to 3,000 mg. daily over the next three weeks. Reserpine and chlorothiazide were added in the fourth week. The regime was continued, but six weeks later the standing B.P. readings had reverted to 200/130 and symptoms of left ventricular failure had recurred. The patient was re-stabilized on pempidine 60 mg. daily with most satisfactory standing B.P. readings of around 150/100.

Comment.—Rapid development of resistance to bretylium tosylate. Recurrence of heart failure from uncontrolled hypertension. Ultimate recourse to ganglion-blocking drugs.

Case 2

A Ganda female market stallholder aged 53 presented with headache, a B.P. of 210/120 mm. Hg. and an atrial gallop. Urine: albumin nil, deposit occasional leucocyte. Blood urea 36 mg./100 ml. E.C.G.: left ventricular hypertrophy. She was stabilized on pempidine 10 mg. daily and reserpine, and had a B.P. of 150/80. She failed in clinic attendance as she had been imprisoned for illicit distillation of spirits. She was transferred from prison to hospital in congestive failure and showed grade 3 retinopathy. The B.P. was 210/100. She was started on bretylium 600 mg. daily, with fair control of the B.P. Four weeks later the dose was gradually increased to 3,000 mg. daily because of tolerance to bretylium. Despite the addition of chlorothiazide the standing B.P. was 230/140 and she was readmitted in congestive failure 10 weeks after commencement of bretylium. She was re-stabilized on pempidine 20 mg. daily with added bendrofluazide. When last seen there were no signs of congestive failure and the B.P. was 150/90.

Comment.—Congestive heart failure precipitated as a result of ineffective control of blood-pressure with bretylium. Final successful recourse to pempidine.

Case 3

A 43-year-old Ganda male civil servant was investigated for insomnia and headache. The B.P. was 170/110. Urine: nothing abnormal. Blood urea 22 mg./100 mg. E.C.G.: left ventricular hypertrophy with T inversion in left ventricular leads. He was successfully treated with pempidine 10 mg. daily and reserpine, the B.P. being 120/100 on most occasions. However, constipation and impotence were disabling. He was changed to bretylium 600 mg. daily. Sexual function was restored when he was seen four months later, but the B.P. had risen to 180/115 and there was deterioration in the E.C.G.—that is, increased T inversion in the left ventricular leads. Finally, he reverted to mecamlamine 5 mg. daily with added reserpine and bendrofluazide. The B.P. fell to 130/80 and the E.C.G. was unchanged.

Comment.—Electrocardiographic deterioration incidental to treatment with bretylium ? related to ineffective blood-pressure control. Satisfactory stabilization with mecamlamine.

Case 4

A 50-year-old Nubian female landholder was first seen in congestive heart failure; B.P. 250/155. Urine: trace of protein, a few red cells, no casts. Blood urea 18 mg./100 ml. Intravenous pyelogram: nothing abnormal detected. E.C.G.: left ventricular hypertrophy and strain. She was stabilized for one year on pempidine 30 mg. daily. The standing B.P. was 130/100 on most occasions, but she complained bitterly of muscular weakness. She was therefore transferred to bretylium, starting with 600 mg. daily. Two weeks later the B.P. was 240/150. The dose was gradually increased to 3,000 daily because of obstinate drug resistance, but eight weeks later the B.P. was 170/130. She was uncomfortable because of great muscular weakness. Bretylium was therefore stopped and she was re-stabilized on pempidine 30 mg. daily. B.P. fell to 140/90, but disability from muscular weakness persisted.

Comment.—Resistance to bretylium. Effective blood-pressure control with use of pempidine at expense of side-effects.

Discussion

A combination of mecamlamine or pempidine, reserpine, and the thiazide agents is a proved effective regime in the treatment of severe hypertension. Excellent blood-pressure control can be achieved without severe side-effects in most patients. In a number the side-effects are so severe as to cause difficulty in management. It is in this group of patients that improved methods of treatment have their place. Moreover, if an effective alternative regime is possible it is desirable to avoid the side-effects of ganglionic blockade.

In our patients transfer to bretylium tosylate was followed by relief of the side-effects of parasympathetic blockade, but in nearly all of them blood-pressure control was not as satisfactory as during treatment with ganglion-blocking drugs. Tolerance to bretylium occurred frequently, and in a number of patients severe resistance to bretylium was apparent in the initial weeks of therapy. For these reasons mecamlamine or pempidine remains the drug of choice.

It is worth while reflecting on possible reasons for tolerance to bretylium. By the use of ^{14}C -labelled bretylium tosylate Boura *et al.* (1959) demonstrated that the drug accumulates in sympathetic ganglia, post-ganglionic fibres, and in general in those organs with a rich adrenergic innervation. Their findings indicate that bretylium produces a fall in blood-pressure by blocking the post-ganglionic sympathetic nervous system. Experimentally, with bretylium as with sympathectomy, Boura *et al.* showed that the effects of injected adrenaline, noradrenaline, or other pressor amines, such as methylamphetamine, are increased. Likewise Laurence and Nagle (1961) have demonstrated in man potentiation of adrenaline and noradrenaline by bretylium.

When increasing doses of bretylium are given it was suggested (Boura *et al.*, 1959; Zaimis, 1961) that pressor effects result from increasing sensitivity of arterioles to the local effects of circulating catecholamines. On this hypothesis an initial good clinical response to bretylium could be followed by increasing tolerance to rising dosage. One might therefore expect that drugs which block the peripheral effects of noradrenaline might prevent the development of tolerance to bretylium or abolish it when present. Lowe's (1961) experiments, however, using phenoxybenzamine hydrochloride ("dibethylene") in patients with acquired tolerance to

bretylium, did not enable any firm conclusions to be drawn. Although his series was a small one, his findings did not disprove nor did they give any support to the view that tolerance to bretylium is due to circulating noradrenaline acting on hypersensitive arterioles.

Side-effects reported in our series of patients were few compared with those reported for other series. Facial pain, occurring with the first few bites of food and accompanied by tenderness of the parotid area, has often been reported with bretylium (Lowther and Turner, 1960; Hurley *et al.*, 1960). It is possible that this and other side-effects were produced in our patients but were missed in the translation of vernacular idiom.

Arising out of our experiences we have learnt that a major risk in change-over from ganglionic blockade to sympathetic blockade with bretylium tosylate is loss of control of blood-pressure resulting usually in a return of severe hypertension with its attendant complications. Where a change-over is desired it should be attempted only under close supervision. Smirk and Hodge (1959) and Hodge and Smirk (1960) have reported on favourable results obtained with a combination of bretylium and a potent ganglion-blocking drug in proportions which reduce the blood-pressure adequately without causing significant parasympathetic side-effects. We have not ourselves tried such a combination, because it would be too complex for our particular community of patients.

Summary

Twenty-nine African hypertensive patients were treated with bretylium tosylate at a hypertension clinic in Uganda. The results in 14 were satisfactory. The high incidence of unsatisfactory response in 15 patients makes bretylium unsuitable for the initial management of hypertension or for the long-term management of patients with severe forms of hypertension.

Until a sympathetic blocking agent which is effective under long-term conditions is available, the potent ganglion-blocking agents mecamlamine and pempidine should be the drugs of choice because their effects are predictable and reliable in the majority of patients with severe hypertension.

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