SYMPATHETIC BLOCKADE IN TREATMENT OF HYPERTENSION **CLINICAL TRIAL OF BRETYLIUM TOSYLATE**

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Ten years ago, in papers on medical sympathectomy and the clinical use of methonium compounds, early experience in this unit with ganglion-blocking drugs was recorded (Turner, 1950, 1951). Recently the indications for treatment, method of administration, and the problems of tolerance and side-effects were reviewed (Turner, 1959).

At an early stage it was decided that to initiate life-long treatment with potent and potentially dangerous drugs was a major decision and that it was best first to make a detailed and standardized assessment of each patient in hospital. If treatment was indicated we tried to achieve a steady state with the appropriate drug, and then further treatment was supervised on a long-term basis in a special clinic organized for the purpose. This procedure has helped to ensure the proper and uniform selection of patients suitable for treatment, has facilitated the maintenance of good control over the blood-pressure as well as the collection and correlation of data, and has made possible comparative assessments of different drugs. Numerous ganglion-blocking agents have been investigated, all potent in lowering the blood-pressure, but none free from difficulties of administration, particularly as regards tolerance and side-effects. None, in fact, has been satisfactory.

Although the blood-pressure can be reduced to almost any desired level this can rarely be achieved without troublesome side-effects from concomitant parasympathetic blockade. Some improvement results from combining the ganglion-blocking drug with chlorothiazide or rauwolfia, but in some degree most patients complain of constipation, dryness of the mouth, difficulty with accommodation, delay in micturition, or impotence. In many individuals these effects are associated with a feeling of general malaise. Because of all this, physicians have looked forward to the day when research workers would be rewarded by the finding of a compound with selective blocking action on the sympathetic nervous system.

Recently, in the laboratories of the Wellcome Foundation in England and the Ciba Foundation in Switzerland, compounds have been isolated which do selectively block the peripheral sympathetic nervous system by accumulating in sympathetic ganglia and post-ganglionic fibres.

The first of these has been given the name of bretylium tosylate ("darenthin"), and has the formula N-o-bromobenzyl-N-ethyl-N,N-dimethylammonium p-toluenesulphonate. The second substance has been

given the name of guanethidine ("ismelin") and has the formula 2-(octahydro-L-azocinyl-ethyl) guanidine sulphate.

This paper is principally concerned with a clinical trial of bretylium, which we have used for 15 months in the treatment of 43 patients with hypertension.

Material and Method

Our selection of cases, measurement of blood-pressure, and general principles of administration have been similar to those previously described and will not be elaborated here. Only those patients were treated who, in addition to high diastolic pressures, had objective evidence of secondary changes in the fundi or heart. Brief clinical details are shown in Table I.

TABLE I.—Clinical Details (43 Cases)

		No. of Cases
Method of Presentation	Left ventricular failure	12
	Cerebro-vascular accident	9
	Headache	7
	Disturbance of vision	6
	Routine examination	6
	Miscellaneous	3
Diastolic Blood-pressure	Blood pressure 130+	40
	" " 120-129	2
	" " 110-119	1
Retinal Changes	Grade 4	8
	" 3	11
	" 2	21
	" 1	3
Left Ventricular Hypertrophy (E.C.G.)	Present	39
	Absent	4
Renal Function	Impaired function	9
	Renal failure	2
	Normal function	32

The blood-pressure was recorded after the fourth consecutive inflation of the cuff. Retinal changes were classified according to the criteria recommended by Keith, Wagener, and Barker (1939). Criteria for left ventricular hypertrophy were those recommended by Sokolow and Lyon (1949). Considerable ventricular hypertrophy may develop before this is reflected in the electrocardiogram. Renal failure denotes a blood urea above 40 mg. per 100 ml. Impaired renal function denotes an endogenous creatinine clearance below 100 litres/24 hours or phenolsulphonethalein excretion below 20% in 15 minutes.

For the purpose of assessing the drug the fall in blood-pressure was taken as the sole criterion of therapeutic effect. Many of these patients had been previously treated with ganglion-blocking drugs. As the basis for selection of patients and general method of treatment in our clinic has been unchanged for ten years we believe it is possible to compare the result of this trial with those previously carried out for other drugs—for example, mecamlamine (Kitchin, Lowther, and Turner, 1957).

The initial dose was 100 mg. (half-tablet), given three times daily after meals, and daily increments of 100-300 mg. were made at intervals of two to three days. In patients who are under close observation in hospital the dose can be increased to 6 tablets a day quite quickly, but caution is necessary because some patients are far more sensitive than others, and we have encountered syncope from postural hypotension with a daily dose as small as 300 mg. On the other hand, some patients are very resistant to treatment, and the daily dose may have to be increased to as much as 3,000 mg. (15 tablets) before the standing diastolic pressure falls significantly. The average daily dose given to our group of patients was 2,000 mg. In one patient the blood-pressure was resistant to 6,000 mg. a day.

Results

The results have been classified into "good," "fair," and "poor" groups. A good result is claimed when the blood-pressure is reduced by 30/20 mm. and the diastolic pressure to below 100 mm. A fair result is claimed when the blood-pressure is reduced by 30/20 mm. and the diastolic pressure to 100/110 mm. Where there was no appreciable hypotensive effect throughout the period of trial the result was graded poor.

On this basis, 8 patients (19%) after an average period of six months show good results, 8 patients (19%) show fair results, and 27 patients (62%) are graded as poor. By the rather less strict criteria described by Dollery, Emslie-Smith, and McMichael (1960) 38% of results would be graded as good, but this entails accepting a reduction of 20 mm. Hg or more as a good result even though the diastolic pressure remained high. By either standard these results cannot be regarded as satisfactory for patients with severe hypertensive disease and for treatment which necessitates frequent visits to a clinic because of the development of tolerance, which imposes a new set of unpleasant side-effects, and which may, after dose increments extending over several weeks, be entirely ineffective owing to resistance. Treatment with bretylium has in fact now been abandoned in 35 (81%) of our patients. It is emphasized that "good" results, by whatever criteria they are judged, represent merely the blood-pressure response and do not imply that bretylium is a satisfactory therapeutic agent in other aspects.

In fact, the major disadvantages of tolerance, variability of response, and syncope render it not only a disappointing hypotensive drug but sometimes also a dangerous one. When the additional disadvantages of side-effects, resistance, and sensitivity are added it is clear why treatment with bretylium has had to be abandoned in so many patients, and our decision not to use the drug for new patients seems amply justified. These disadvantages merit consideration in rather more detail.

Tolerance

Boura *et al.* (1959), in their original paper, predicted that tolerance was likely to develop. Our experience and that of others has shown that this effect, despite the advantages of freedom from parasympathetic blockade, largely vitiates the value of the drug.

Graph showing five examples of tolerance. The starting-point in each case is dose required to produce initial normal B.P.

A preliminary fall in pressure occurs in most cases, but when kept under observation for several months a high proportion of patients (74%) required a steady increase in dose in order to maintain control, if indeed control could be maintained. Patients treated with bretylium must thus continue under the close supervision which has been necessary with other drugs. Despite reassurance, these repeated increases inevitably engender disappointment and depression at successive attendances, and when side-effects are also troublesome much persuasion is required to induce patients to continue. In addition, repeated visits to hospital at short intervals lead to administrative difficulties in running the clinic.

As can be seen from the Graph, tolerance tends to develop early and to increase at varying speeds. Thus, for these patients it is not advisable to extend the period between visits beyond a few weeks. Apart from these disadvantages, tolerance results in ineffective treatment over long periods, and in the end, despite perseverance by patient and doctor, control is often lost. In patients with severe hypertensive disease delay in controlling the blood-pressure may be dangerous.

The rapid development of tolerance may lead to sudden loss of control between visits to the clinic, with serious consequences in patients with severe hypertension. Two of our patients died on this account. It may be, as has been suggested, that some degree of tolerance is inevitable with drugs acting at the neuromuscular junction, but initial experience with guanethidine suggests that with other compounds it may at least be less.

Our early experience in regard to tolerance (Turner and Lowther, 1959) was soon confirmed by others (Evanson, 1959; Dollery, 1960; Dollery *et al.*, 1960; Somers, 1960), and since then numerous workers with whom we have compared experience have noted the same effect.

Variable Response

In some patients, probably owing to varying absorption, the blood-pressure fluctuates considerably from hour to hour, and, as a result, symptoms arising from hypotension may appear unpredictably and lead to feelings of insecurity and apprehension. We have made estimations of the blood-pressure at hourly intervals in patients on bretylium, and have found on many occasions swings of pressure which make it clear that it is impossible to control dosage with reference to single pressure estimations such as may be recorded in the consulting-room or out-patient clinic, even if pressure is recorded at the same time of day on each occasion. This is of especial importance in those patients in whom dosage is critical, and in whom even a small change may result in considerable alterations of the blood-pressure. Examples of instability of response are shown in Table II.

It is emphasized that our recordings are taken under uniform circumstances and by the same observer after the patient has been standing for a period of three minutes.

TABLE II.—Showing the Variations in Standing Diastolic Blood-pressure (mm. Hg) from Hour to Hour in 7 Patients Taking Bretylium

	1	2	3	4	5	6	7
10 a.m.	140/110	140/105	170/95	140/115	180/115	190/115	200/140
11 "	100/80	200/120	170/115	175/125	130/95	200/125	150/115
12 noon	110/95	130/95	195/125	175/145	150/115	180/105	180/135

Syncope

Syncope must be included amongst the major disadvantages of bretylium, and in our experience is more troublesome than with any other drug, principally because it may develop so rapidly and quite apart from postural hypotension. Syncope, especially on exertion, may occur without warning, and potentially is exceedingly dangerous. It has occurred in six of our patients. One woman walked up five flights of stairs in a department store and lost consciousness at the top. An actuary left the clinic feeling well, walked down the drive, and hurried over the road to catch a bus. He suddenly lost consciousness and was nearly run over. Two others fell down in the street. Another patient, while sitting in a chair, twice lost consciousness, which, although relatively safe, caused great anxiety. In none of these patients was the standing diastolic pressure, when last recorded, below 115 mg. Hg. Other workers have reported similar effects (Lowe and Rosenheim, 1960).

Evidence that exertion may lead to a sharp fall in cardiac output in patients taking bretylium has recently been presented by Taylor and Donald (1960), and it seems that this is the causal mechanism in some patients. In other cases exertion has not been involved, and the mechanism here is more obscure. We have not seen dangerous complications from postural hypotension, but others have been less fortunate (Dollery *et al.*, 1960).

Side-effects

Side-effects, though numerous and often troublesome, are relatively mild compared with those which are associated with ganglion-blocking drugs, and it is this fact which gives rise to initial enthusiasm in patients who are transferred from one drug to the other.

The registration of side-effects is one in which individual practice varies widely. Some believe that the patient should be asked only in general terms how he or she feels, and that questioning at once obtrudes the beliefs and prejudices of the observer. Others approach the patient armed with a list of potential side-effects, and lay themselves open to the charge of suggestion. While there is no doubt that the frequency of any observation depends on the diligence with which it is sought, it is unlikely that many patients actually fabricate complaints, and if the numbers under observation are large enough and the symptoms are of similar type this latter objection becomes of little importance. We ourselves approached patients on bretylium with no set idea of what side-effects might occur, and indeed early in our experience attributed certain complaints to neurosis. It was only as these recurred with increasing frequency and fell into the same patterns that it became obvious that the effects were attributable to the drug. Subsequently some patients were questioned more directly—for example, as to whether any effect had been noticed on bowels or bladder or any odd sensations about the body. It became clear that many patients had not mentioned side-effects because they had regarded them as irrelevant, and others were more impressed by relief from the unpleasant effects of ganglion-blocking drugs.

Side-effects occurred in 39 out of the 43 patients, and would often have been tolerated if bretylium were a more effective hypotensive agent. Side-effects are generally more frequent in the early stages of treatment, and tend to diminish in importance as time passes. This

may, of course, be due to the fact that the patient learns to live with them, and accordingly they slip below the threshold of consciousness. Certain complaints, however, are painful and persist, and may become worse with successive increments in dosage. This is particularly true of parotid pain. About twenty different side-effects have been reported, and our patients have experienced most of them (Table III).

TABLE III.—*Side-effects of Bretylium (43 Cases)*

Symptoms	No. of Cases
Dizziness (not due to posture)	23
Chest constriction or paraesthesiae	15
Frequency of micturition	15
Parotid pain	17
Dyspnoea	13
Diarrhoea	9
Headache	11
Muscular weakness	12
Syncope	6
Nasal congestion	12
Sweating	7
Tinnitus	4
Sexual difficulties	2
Nausea	2
Psychosis	1
Nil	4

Dizziness is a frequent complaint which is not related to postural hypotension, and not always to exertion. The cause may not be the same in all cases. The fall in blood-pressure caused by exertion in patients taking bretylium, to which attention was first drawn by Lowe and Rosenheim (1960), is a likely cause in some, and further exercise might result in syncope. In others, however, dizziness may occur while at rest or when doing nothing in particular. Dizziness tended to occur most often in the early stabilization stage of treatment, but it does tend to recur with any increment in dose in some patients, and eventually may prevent reaching the dose required to achieve full control of the blood-pressure.

Constriction in the chest is an unpleasant sensation which may simulate angina pectoris, but we have not yet been able to demonstrate evidence of myocardial ischaemia, and in most cases the probable cause lies in the chest wall. *Paraesthesiae*, especially in the form of "hot" sensations in the skin, are common over the front of the chest, but may also occur elsewhere.

Frequency of micturition is a common complaint and occurs usually at night in both men and women. This complaint tends to persist, but has not been sufficiently troublesome to require stopping the drug.

Parotid pain is a new and interesting drug-effect which has troubled about 40% of our patients. It is one of the symptoms which may persist beyond the stabilization period, and, in fact, is relatively infrequent in the early stages. Pain is centred just behind the mandible, and usually occurs once with the first bite of a meal or even of a sweet, and lasts for only a few seconds. It is occasionally of considerable severity. It cannot be produced by mere clenching of the teeth, nor is it produced by anticipation of food. There is no subjective increase in salivation. The pain occurs at rest, and there is no relationship to fall in blood-pressure.

Some patients have a continuous dull ache with tenderness in the region of the parotid gland. Patients who develop tolerance may nevertheless continue to complain of pain. Pain may persist for weeks or months if treatment is changed to guanethidine, and we know of one patient in whom it has persisted for several months after stopping all treatment. The mechanism of parotid pain is at present obscure. The

most likely explanation would seem to lie in increased secretion against resistance, such as might be produced by contraction of the smooth muscle in the duct, but it is difficult to fit in all the features mentioned above. We understand that attempts are being made to solve the problem by pressure-flow studies.

Dyspnoea on effort is a definite entity which occurs in about 30% of patients. There is no complaint of paroxysmal dyspnoea, nor is there any radiographic evidence of pulmonary oedema. No evidence of bronchospasm has been found on clinical examination, but one patient specifically complained of wheezing. The dose producing this side-effect may be critical, and in some patients the effect can be made to appear and then disappear by adding and withdrawing as little as 300 mg. of the drug daily. Dyspnoea may appear as an augmentation of existing dyspnoea or it may arise in a patient with no previous history of breathlessness. Pulmonary function and haemodynamic studies may well elucidate the pathogenesis of this symptom. Taylor and Donald (1960) have shown in acute experiments that bretylium may induce considerable pulmonary arterial hypertension.

Diarrhoea.—In striking contrast to the effects of ganglion-blocking drugs, some looseness of the bowels may occur, but this has not been severe or of such frequent occurrence as with guanethidine.

Headache may be produced in patients who had not previously had this complaint as a manifestation of their hypertension nor had been particularly subject to it in the past. In some it tends to persist.

It is noteworthy that certain of the complaints tabulated are those which might be expected to occur as a result of parasympathetic overactivity. Side-effects may also vary from patient to patient but tend to continue in the same pattern for each patient. These facts recall the observations of Paton and Steinberg (1956), who injected hexamethonium into 50 students from University College Hospital. Objective studies were made as regards ten autonomic tests, and the pattern of response was found to be different in every one. The similar variation in response which was found clinically with bretylium also reflects the difference in autonomic constitution between individuals.

Muscular Weakness.—This is an interesting complaint which can probably be explained on the basis of the experimental observations of Boura and Green (1959), in which it was shown that in rats and in cats paralysis occurred at the neuromuscular junction, and that when bretylium was given in a dose of 50 mg./kg. to monkeys muscular power was decreased.

Mental Changes.—One patient in our group previously unaffected by any form of mental instability developed a severe anxiety state, with depression, on being changed from pempidine to bretylium, and had to be admitted to a mental hospital. There has been no recurrence on guanethidine. Other workers have experienced a higher incidence of mental changes (Evanson and Sears, 1960).

Sexual Difficulties.—We have not made a particular point of inquiring about sexual difficulties, and few patients make spontaneous observations on this aspect. However, one practitioner noted undoubted and very considerable reduction in the volume of semen, one patient was much disturbed by loss of libido, and another by impotence.

Resistance

Resistance occurred in three patients, all with severe hypertension. This implies that there was no fall in standing blood-pressure despite a steady increase of dose to high levels—6,000, 4,800, and 3,000 mg. respectively. The effect of this practical defect was waste of time and the risk of potential complications from continued hypertension, and in the end a new drug had to be used.

Sensitivity

Exceptional sensitivity occurred in three patients, and in each a profound fall in blood-pressure resulted from a dose of 100 mg. (half-tablet) three times daily. It is therefore important to start with a small dose, such as 100 mg. twice daily, and gradually work up.

Bretylium in Combination

In four patients in whom control was impossible on bretylium alone, pempidine was added in small doses (2½–5 mg. t.d.s.). Larger doses were not used because of the development of side-effects from parasympathetic blockade. As a result control of the blood-pressure became classified as good in two, fair in one, and one was unchanged at poor. In four other patients chlorothiazide was added in a dose of 250 mg. three times daily, but this combination failed to influence the pressure to an appreciable extent. We did not persevere with this combination owing to the disadvantages of bretylium.

Guanethidine

After six months of a pilot trial it became clear that bretylium was not a suitable preparation for the treatment of the majority of patients with severe or moderately severe hypertension. Accordingly it was decided to continue only with those in whom it was still proving reasonably satisfactory and gradually to switch the others to guanethidine. By this means the effects of the two drugs could be compared in the same patients. It was also decided to start a pilot trial of guanethidine in patients with hypertensive disease of similar severity to those begun on bretylium.

Now after more than twelve months' experience with bretylium and six months' experience with guanethidine it seems probable that the latter preparation, though not ideal, is superior, and that a formal comparative trial would not be profitable or justifiable.

So far tolerance has been less troublesome and side-effects milder with guanethidine than with bretylium, and almost all patients who have had both drugs prefer the former. Experience is too limited in time and the numbers of patients too small to be dogmatic about the absolute value of guanethidine. Nevertheless, our present impression is that guanethidine is a better preparation for the treatment of hypertension, but in relatively resistant cases and in those who develop looseness of the bowels it should be combined with a ganglion-blocking drug in small dosage. It has not been established that for severe cases it is superior to a combination of a ganglion-blocking drug with chlorothiazide.

Conclusion

There is no doubt that the advent of a blocking substance with a selective action on the sympathetic division of the autonomic nervous system is an important event in physiological research, and from the pharmacological aspect opens up possibilities for a new

era in treatment. From the clinical point of view bretylium tosylate itself has proved disappointing.

In a series of 43 patients tolerance has been experienced in two-thirds, bringing attendant failure, disappointment, and even death as the patient passes out of control. We have found exceptional sensitivity in some, which indicates that treatment must be begun with a very small dose at first, and exceptional resistance in others, which results in the waste of weeks or months in hospital while stabilization is sought with a steadily increasing dose. We have found many side-effects which might be bearable were the treatment more effective, but which, combined with tolerance, sensitivity, and variable absorption must convince the most optimistic that in bretylium there is no new hope for hypertensive patients. In particular, recurrent dizziness and syncope are effects which no clinician can be willing to impose upon his patient.

While bretylium will produce a fall in blood-pressure in almost all patients the pressure can be safely and comfortably maintained at reasonable levels in only a very few, and certainly not in those with severe or malignant hypertension. We certainly agree with the Hammersmith workers that bretylium is not the drug of choice for patients with severe hypertension. Since none of the more potent drugs yet produced is sufficiently safe or free from side-effects to justify treating patients with mild hypertension, the only ones for whom it might be considered are those with hypertensive disease of moderate severity or in whom only a moderate lowering of blood-pressure is desirable. However, tolerance develops so frequently that treatment should not be persisted in for long. Thus, although the research workers can be congratulated for their breakthrough into a new field of autonomic blockade, bretylium tosylate is not a practical and effective therapeutic agent, and may, in fact, jeopardize the patient's life. In our opinion it should not be used for the treatment of hypertension. Initial experience with guanethidine has been more encouraging.

Summary

Forty-three patients with hypertension of a severity sufficient to cause secondary changes in the retinae or heart have been treated with bretylium tosylate for an average period of six months.

A short-lived fall in blood-pressure was usually found, but in two-thirds of these patients tolerance developed and the blood-pressure rose again despite steady increases in dose.

Side-effects were frequent, including dizziness, parotid pain, dyspnoea, and syncope, the last being a potentially dangerous end-result.

Some patients showed sensitivity to doses of 100 mg. t.d.s., and a few were resistant to doses rising to 6,000 mg. daily.

It is concluded that bretylium tosylate should not be used for the treatment of hypertensive patients.

Our thanks are due to Miss Norma Millar, our technician, who recorded with painstaking accuracy and good humour the very large numbers of blood-pressure readings upon which this study is based.

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CEREBROSPINAL FLUID GAMMA-GLOBULIN IN MULTIPLE SCLEROSIS

OBSERVATIONS ON ITS NATURE

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It has been known for some time that the gamma-globulin level in the cerebrospinal fluid of cases of multiple sclerosis is commonly raised (Kabat, Moore, and Landow, 1942; Yahr, Goldensohn, and Kabat, 1954; Volk, Saifer, and Rabiner, 1954). It has been suggested that the rise may in part result from antibody formation within the central nervous system (Kabat, Moore, and Landow, 1942; Kabat, Freedman, Murray, and Knaub, 1950), though direct evidence of this is not available. The antiglobulin consumption test introduced by Steffen (1954) is capable of demonstrating increased globulin in the spinal fluid in multiple sclerosis, and in the present paper the ability of this excess globulin to fix to brain substrate has been examined.

Material and Methods

Spinal fluids of eight cases of acute exacerbation of multiple sclerosis and of 24 chronic cases have been tested.

A suitable specimen (clear of all blood) was diluted 1 in 16 times. Dilutions of a Coombs serum (final titre 1 in 2,048) from 1:16 to 1:512 were prepared and single drops plated out on to a clean glass plate. To each, one drop of the diluted spinal fluid was added. Interaction, aided by occasional gentle agitation, was allowed to take place for five minutes at room temperature. One drop of sensitized Group O Rh+ cells was then added to each mixture and any agglutination recorded at five and again at ten minutes. The globulins of the spinal fluid reacted with some of the Coombs reagent so that its original titre was reduced.

A suspension of normal human white matter was prepared by cutting frozen sections of the fresh tissue at 30 μ , and disrupting these in saline in a blender. The finely dispersed material was washed eight times to