Selective Inhibition of the Sympathetic Nervous System in Man with Bretylium Tosylate, a New Antihypertensive Agent

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Boura and his associates have demonstrated that bretylium tosylate (Daren-thin)* produces a selective block of the sympathetic nervous system.1 This benzyl quaternary ammonium compound appears to accumulate preferentially in peripheral sympathetic neurones. Unlike adrenergic blocking agents the effects of released or injected epinephrine and norepinephrine are not antagonized, and unlike ganglion-blocking drugs the parasympathetic nervous system is not inhibited at therapeutic dose levels of bretylium.1 Clinical trials in hypertensive patients indicate that orally administered bretylium tosylate causes a predominantly orthostatic fall of blood pressure comparable to that achieved with the ganglion-blocking drugs but without the side effects of parasympathetic blockade.1,2 The following report summarizes our experience to date with this new agent.

Inhibition of Sympathetic Vasoconstrictor Reflexes

The reflex activity of the sympathetic vasoconstrictor system was assessed in normotensive men as follows: 1. TheValsalva “overshoot” of arterial pressure was recorded directly with a strain gage from a needle placed in the brachial artery. After a deep inspiration the subject blew forcefully and steadily into a closed tube for 10 seconds to produce a sustained increase in intrathoracic pressure. The expiratory effort was then suddenly and completely released. The resulting “overshoot” of arterial pressure has been shown to be due to a reflex sympathetic discharge occurring during the period of diminished cardiac return and, hence, cardiac output.3 2. The cold pressor response was recorded by placing the patient’s hand in a mixture of water and ice for 1 minute. 3. Reflex sympathetic vasoconstriction in the digit was recorded from a plastic cup sealed to a finger and attached through a short length of plastic tubing to a sensitive strain gage (digital plethysmograph). The decrease in pulse and finger volume indicating vasoconstriction was recorded following the stimulus of a deep breath. The latter has been shown to initiate a reflex sympathetic discharge to the digit. Following the control determinations of the sympathetic reflex responses, which were carried out with the subjects resting supine in a warm room, bretylium tosylate diluted in isotonic saline to a final concentration of 15 mg. per ml. was injected slowly intravenously over a period of 4 minutes. No subjective side effects were complained of during or following the injection. Dosages of 50, 100, and 150 mg. were given in different subjects.

Partial inhibition of the sympathetic vasoconstrictor reflexes appeared at a dose level of 50 mg. (approximately 0.7 mg. per Kg.) of bretylium tosylate intravenously. Complete inhibition of the Valsalva “overshoot” (fig. 1) and of the digital vasoconstrictor response to a deep breath (fig. 2) was accomplished at a dose level of 150 mg. (approximately 2 mg. per Kg.). This is comparable to a dose of 50 mg. of hexamethonium chloride intravenously, which produces a similar blockade of these reflex responses.4

The cold pressor response was inhibited but not completely blocked by bretylium tosylate even in doses of 150 mg. (fig. 3). By contrast, hexamethonium 50 mg. intravenously, usually

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Footnotes:
Figure 1
Recordings of arterial pressure illustrating abolition of the vasopressor “overshoot” following the Valsalva maneuver in a 38-year-old Negro man with essential hypertension. During interval between arrows on the baseline the patient blew forcibly into a closed tube. In the control period (upper tracing) following release of the expiratory effort note hypertensive “overshoot,” indicated by the upper arrow. After 150 mg. of bretylium tosylate intravenously (lower tracing) the overshoot was abolished.

blocked this response completely. The cold pressor test, however, is a complex response involving not only an immediate reflex vasoconstriction but also a delayed pressor effect, which may be due to adrenal discharge. In this connection Boura has reported that in animals bretylium, unlike the ganglion-blocking drugs, does not block the adrenal discharge of catecholamines following sympathetic stimulation. It is possible that the failure to block the delayed response of the cold pressor test in man is due to this phenomenon.
Figure 2

Recordings of digital plethysmograms in a 41-year-old man with essential hypertension. In the control period (upper tracing) following a deep breath a vasoconstrictor response occurred in the digit as indicated by diminution of both pulse and digit volume. Following 150 mg. of bretylium tosylate intravenously this reflex vasoconstrictor response was abolished (lower tracing).

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Orthostatic hypotension was minimal at the 50-mg. dose, but moderate to severe at the 100-mg. level. This result is similar to our previous experience with hexamethonium, that only partial inhibition of sympathetic vasoconstrictor reflexes is required to produce significant orthostatic hypotension.

**Dose-Response Relationships**

Effective intravenous doses were defined as the amount required to produce a significant orthostatic hypotension. In 4 hospitalized hypertensive subjects tested this dose varied between 50 and 150 mg. Orthostatic hypotension appeared within 10 minutes after the intravenous dose. The supine blood pressure was only moderately affected by these dosages. There were no side effects except for slight postural faintness.

On subsequent days bretylium tosylate was administered orally in increasing dosages once daily in the morning until significant orthostatic hypotension occurred. This was done in an attempt to establish a relationship between parenteral and oral dosages. The ratio between effective oral and intravenous dosages varied between 8 to 1 and 24 to 1 in different patients. Since bretylium is a quaternary ammonium compound it was not surprising that absorption was poor after oral administration.

**Therapeutic Results in Hypertensive Patients**

Sixteen ambulatory patients with moderate to severe hypertension who had been under prior treatment with other agents were treated with bretylium tosylate for periods varying from 1 to 5 months. Bretylium was given alone in 8 patients. In the remainder it was substituted for a blocking agent without changing the adjunctive medication, which consisted of chlorothiazide or hydrochlorothiazide and in 2 patients of small doses of hydralazine. Administration of bretylium was begun at a dose of 200 mg. 3 times daily; after breakfast, at 2 p.m., and 10 p.m. (600 mg. daily). Modification of dosage was then made upward or downward, depending on the response of the blood pressure. In 11 patients blood pressure levels were recorded usually in the sitting and erect positions twice daily in the home.

Effective antihypertensive dosage varied widely in different patients. In the group without adjunctive therapy, 600 mg. of bretylium daily was the lowest effective dose and 3,000 mg. the highest. Several patients, however, failed to exhibit an antihypertensive effect on 3,000 mg. per day. Efforts to raise the dosage above this level were not attempted because of the large number of tablets required.

In the patients receiving adjunctive therapy (primarily chlorothiazide) 200 mg. of bretylium tosylate was the smallest effective daily dose, whereas one patient failed to exhibit significant orthostatic hypotension on 3,000 mg. daily. Although the series is too small for accurate appraisal of the average dose, the majority of the patients who responded exhibited moderate reduction of supine blood pressure and definite but tolerable orthostatic hypotension in a dosage range of 1,800 to 2,400 mg. without chlorothiazide and 1,000 and 1,200 mg. with chlorothiazide.

The only side effects encountered that could be attributed to bretylium tosylate were orthostatic faintness similar to that encountered with the ganglion-blocking drugs, and failure of ejaculation in a few male patients similar to that encountered after guanethidine. Several patients complained of tenderness over the parotid glands with pain in these areas on mastication. Orthostatic hypotension with faintness and weakness tended to occur most commonly in the morning, and for this reason the morning dose was given after rather than before breakfast. As with the ganglioplegic agents careful dosage adjustment and periodic readjustment were required to obtain blood pressure control on the one hand and avoid postural faintness on the other. Parasympathetic blocking effects such as constipation, dryness of the mouth, difficult micturition, and failure of visual accommodation were entirely absent. Diarrhea, which may occur after guanethidine, was not noted by the patients taking bretylium. The heart rate did not change significantly, and there were no arrhythmias. Evidences of "tolerance" were simi-
Figure 3
Recordings of arterial pressure during the "cold pressor" response in a 32-year-old normal man. The subject's hand was immersed in ice water during the 1-minute period indicated by the baseline arrows. As compared to control response (upper tracing) onset of pressor effect was delayed after 150 mg. of bretylium tosylate intravenously (lower tracing) but not completely blocked.

lar to those encountered with the ganglion-blocking drugs. For example, some patients were responsive initially to smaller dosages than were required for long-term control of the blood pressure. Also, with continued treatment there tended to be a narrowing of the early, wide spread between the blood pressure in the supine and erect positions.
Discussion

In general, the present observations confirm those of the prior British investigators.\textsuperscript{1,2} The principal advantage of bretylium tosylate is its lack of parasympathetic blocking action. However, it shares with the ganglion-blocking agents the ability to produce orthostatic faintness and collapse, plus a wide dose-response range in different patients. In order to achieve optimal results these characteristics necessitate painstaking and individualized dosage adjustments similar to those required with the ganglioplegic drugs. This difficulty suggests that bretylium tosylate will be used more advantageously in patients with severe disease whose hypertension cannot be controlled satisfactorily with chlorothiazide, either alone or with small dosages of hydralazine or reserpine. In these patients the ability of bretylium to produce an inhibition of sympathetic vasoconstriction comparable to that achieved with the ganglioplegic agents but without their parasympathetic blocking effects is a definite advantage. Present results suggest, however, that more potent drugs (guanethidine or ganglion-blocking agents) must be substituted in those patients who remain unresponsive to bretylium tosylate in dosages within a practical, clinically acceptable range.

Bretylium tosylate differs somewhat from guanethidine, which also produces a selective blockade of the peripheral sympathetic system.\textsuperscript{5-8} The latter agent produces bradycardia and diarrhea, both of which can be blocked with atropine or similar agents suggesting parasympathetic predominance. Another disadvantage of guanethidine is its prolonged duration of action. At a given dose level the maximum antihypertensive effect may not occur until 4 or 5 days; and after a hypotensive episode, disabling orthostatic effects may persist for several days. This cumulative action of guanethidine requires that elevations of dosage must be accomplished at weekly rather than daily intervals if hypotensive reactions are to be avoided.

Since bretylium has a shorter duration of action averaging about 8 hours, rapid dosage adjustment is permissible and the effects of an overdose are not unduly prolonged. On the other hand, the high dosage requirement is a disadvantage of bretylium tosylate that is aggravated by the failure to produce a tablet containing more than 200 mg. of the drug. Ingestion of more than 3 tablets 3 times daily is psychologically disturbing to most patients. Concomitant administration of chlorothiazide usually permits reduction in the dosage requirement of bretylium to a tolerable range, but this was not true in all cases. In addition to chlorothiazide Smirk and Hodge\textsuperscript{2} have added one of the more potent ganglioplegic drugs in such instances, thus providing an effective but somewhat complicated regimen. It is hoped that further developments will result in a peripheral sympathetic blocking drug that combines the tablet potency of guanethidine with the lack of either parasympathetic blocking or enhancing effects of bretylium.

Summary and Conclusions

Bretylium tosylate inhibited sympathetic vasoconstrictor reflexes in man, but unlike the ganglioplegic drugs it produced no parasympathetic blocking side effects. As with other quaternary ammonium salts the drug was poorly absorbed from the gastrointestinal tract.

Administered orally to hypertensive patients, bretylium tosylate produced a reduction of blood pressure that was primarily orthostatic. Dosage requirements in general were large and in some instances were so excessive as to be therapeutically impractical. Effective dose levels could be reduced somewhat by the addition of chlorothiazide. The only side effects or toxic reactions encountered were postural faintness and syncope (the avoidance of which required scrupulous care in dosage adjustment), pain and tenderness over the parotid glands, and failure of ejaculation in a few patients.
BRETYLIUM TOSYLATE

Summario in Interlingua
Tosylato de bretylium inhibiva sympathic reflexos vasoconstrictori in humanos, sed—per contrasto con le drogas ganglioplegic—illo produceva nulle effecto lateral de blocage parasymptomatic. Como es etiam le caso in altere sales quaternari de ammonium, le droga esseva mal absorbite ab le vías gastrointestinal.

Administrante per via oral a patientes hypertensive, tosylato de bretylium produceva un reduction del tension sanguine que esseva primariamente orthostatic. Le requirimentos del dosage esseva generalmente grande. In certe casos illos esseva si excessive que le therapia deveniva impracticable. Le nivellos del dosage efficace poteva esser reduite in un certe mesura per le addition de chlorothiazida. Le sol adverse effectos lateral o reactiones toxic esseva debilitate postural e syncope. Pro evitar iste ultime, le plus scrupulose attention debeva esser prestate al adjustment del dosage. In plure patientes dysfunction del ejaculation esseva notate.

References

On Cardiac Murmurs
By Austin Flint, M.D.

Case 2. In February, 1861, I was requested to determine the murmur in a case at the Charity Hospital, New Orleans. I found an aortic direct and an aortic regurgitant murmur, both murmurs being well marked. There was also a distinct pre-systolic murmur within the apex, having the blubbering character. On examination after death, the aorta was dilated and roughened with atheroma and calcareous deposit. The aortic segments were contracted, and evidently insufficient. The mitral curtains presented no lesions; the mitral orifice was neither contracted nor dilated, and the valve was evidently sufficient. The heart was considerably enlarged, weighing 17½ oz., and the walls of the left ventricle were an inch in thickness.—Am. J. M. Sc. n.s. 44: 29, 1862.
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