BRETYLIUM & GUANETHIDINE

Two New Drugs Producing Specific Blockade of the Sympathetic Nervous System

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The purpose of this communication is to acquaint practicing physicians with a new class of antihypertensive agents. The ganglion blocking drugs are recognized as the most potent and reliable antihypertensive agents presently available. In clinical practice, however, their use is attended by a high incidence of side effects. Ganglioplegic drugs inhibit transmission through all autonomic ganglia, parasympathetic as well as sympathetic. Such side effects of parasympathetic blockade as paralysis of visual accommodation, dryness of the mouth, and constipation have contributed to the discomforts patients frequently experience with these agents. Since, as far as is known, the antihypertensive effects of these drugs result entirely from blockade of the sympathetic and not at all from blockade of the parasympathetic system, new agents have been sought which would block transmission only through sympathetic nerves.

As often happens, two such drugs have been discovered practically simultaneously, one in England, the other in this country. The British compound is bretylium tosylate (Darenthin®). The American drug is guanethidine (Ismelin®). Both agents seem to block transmission at or near the sympathetic nerve endings. They do not block at the ganglia and they apparently have no inhibiting effect on parasympathetic transmission. Unlike the adrenergic blocking agents such as tolazoline and phentolamine, they do not neutralize or reverse the pressor effects of circulating epinephrine and norepinephrine. They represent, in truth, a new class of compounds whose blocking effects seem to be limited to transmission of sympathetic nerve impulses.

**guanethidine**

The pharmacology of guanethidine was described in 1959. Maxwell and associates found that the drug lowered blood pressure in hypertensive animals, blocked transmission through postganglionic sympathetic but not parasympathetic nerves, and did not prevent the pressor effects of injected norepinephrine. In addition, they reported an unusually long duration of action. The effects of a large, single dose were found to last for one week or longer.

Clinical trials in several clinics quickly confirmed the fact that guanethidine was a potent antihypertensive agent in doses of 25 to 200 mg. per day, depending on the responsiveness of the patient. Postural hypotension resulted, although blood pressure was reduced to a lesser degree in the supine position as well, similar to effects of the ganglion blocking drugs; however, unlike the latter, side effects of constipation, loss of visual accommodation, dry mouth, and difficulty in emptying the urinary bladder were entirely absent. Indeed, diarrhea, which may be caused by unopposed parasympathetic activity, has been a common side effect. Bradycardia has been another evidence of parasympathetic predominance. Libido and erection are not affected although ejaculation which is a sympathetic function may not be consummated.

The long duration of action of guanethidine has necessitated certain precautions in adjusting dosages. Since the duration of action spans a period of approximately one week the daily dosages given during that period will, to a certain extent, be cumulative. Therefore, in ambulatory patients it has been found to be

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**Chemical Structure of Guanethidine and Bretylium Tosylate**

![Chemical Structure of Guanethidine and Bretylium Tosylate](image-url)
prudent to wait at least one week before elevating the
dose level. When dosages were raised more rapidly
orthostatic hypotension and collapse could be precipi-
tated, and sometimes they lasted for four or five days
after the drug was withdrawn. This, of course, is a
more important problem in ambulatory than in hos-
pitalized patients. In the former, dosage increases
should be planned so as gradually to approach a ther-
apeutic maintenance level, at which daily destruction
and excretion equal the daily intake.

**bretyllium tosylate**

At about the same time that findings with guanethi-
dine were announced a group of British investigators
published their report that bretyllium tosylate, a com-
 pound which is chemically wholly different from
guanethidine, also produced selective block of the
sympathetic nervous system. Administration of the
isotopically labeled compound showed that it was in-
corporated into sympathetic nerves in higher concen-
tration than in other nervous tissue.

Clinical trials of bretyllium first in England and then
in this country indicated that the drug produced pre-
dominantly a postural hypotension and that it was
free of the side effects of parasympathetic blockade.
It was poorly absorbed from the gastrointestinal tract
so that large doses, sometimes exceeding 300 mg. per
day, were required. Unlike guanethidine, the duration
of action of the drug was approximately eight to twelve
hours, so that dosages could be administered every
eight hours and elevated fairly rapidly to the effective
level without danger of precipitating a prolonged hypo-
tensive episode. Also, unlike guanethidine, the side
effects of parasympathetic predominance—diarrhea
and bradycardia—did not occur.

Among the principal shortcomings of bretyllium are:
(1) an unusually wide range of dose responses (from
300 to over 3000 mg. per day in divided dosage) in
different patients; (2) lack of antihypertensive poten-
cy in more severe and resistant cases; and (3) develop-
ment of tolerance in some patients. A side effect pec-
culiar to this drug has been the development of bi-
lateral pain and tenderness but without swelling, heat,
or redness in the region of the parotid gland. The
cause is unknown and it most often occurs when dos-
ages are elevated to levels of two or more grams per day.

**general comments**

The antihypertensive effect of both of these agents
is primarily orthostatic. In this respect they are similar
to the ganglion blocking agents in that the blood pres-
 sure in the supine position is the least affected by the
drug. The only advantage of guanethidine and brety-
lium is the absence of parasympathetic blocking effects.

Just as chlorothiazide and other saluretic agents have
enhanced the effectiveness of the ganglion blocking
drugs so have they also been used to advantage with
bretyllium and guanethidine.

It is still too early to say how important a place
these agents will have in the clinical management of
patients with hypertension or to be detailed and spe-
cific about the most effective means for administering
these drugs. Probably they represent promising fore-
runners of better agents to come which will combine
the potency of the ganglion blocking drugs without
their parasympathetic blocking effects.

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