Systemic Hemodynamic Effects of Bethanidine in Essential Hypertension

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SUMMARY
Although available elsewhere, bethanidine remains under study in the U.S. and its hemodynamic effects are unreported. Therefore, 29 patients with moderately severe essential hypertension received one of four oral dose levels (0.10, 0.25, 0.35, or 0.50 mg/kg) of the postganglionic sympatholytic drug. Blood pressure was reduced only in the 14 patients receiving the highest dose. This was demonstrated within three hours, first by a significant postural hypotension (upright tilt: +4 before vs -19 mm Hg after, \( P < 0.001 \)). This orthostatic hypotensive effect was associated with a greater fall in cardiac output (13 vs 22%, \( P < 0.025 \)) and a diminished reflexive increase in total peripheral resistance (19 vs 6%, \( P < 0.01 \); an attenuated Valsalva maneuver overshoot in the supine position was also observed (42 vs 10%, \( P < 0.001 \)). Eight of these 14 patients demonstrated supine hypotension associated with either reduced output and/or resistance. Hence, bethanidine is a rather rapidly acting oral sympatholytic agent which reduces blood pressure by producing: (1) decrease in venous return (especially in upright position), suggesting venodilation; (2) arteriolar dilation (supine and upright) reducing peripheral vascular resistance; and (3) attenuated cardiovascular sympathetic reflexive adjustments.

Additional Indexing Words

Hemodynamics of hypertension
Adrenergic reflexes
Cardiac output
Postganglionic sympathetic inhibition
Antihypertensive therapy

SYMPATHOLYTIC DRUGS have become a cornerstone in the basic management of patients with hypertension of moderate to severe vascular disease. Thus, with the development of ganglion blocking, postganglionic, and centrally acting adrenolytic agents, cardiovascular mortality and morbidity in these patients have improved dramatically. Two drawbacks to the postganglionic inhibiting compound guanethidine are its delay in onset of action when rapid control of blood pressure is necessary and its slow disappearance of action when undesired effects have arisen. Bethanidine, a new postganglionic neuronal blocking agent with an action very similar to guanethidine, has enjoyed broad clinical experience outside of the United States. However, despite this general use, systemic hemodynamic studies in man remain unavailable. This report is concerned with the immediate systemic hemodynamic effects of bethanidine in patients with essential hypertension of moderately severe vascular disease.

Materials and Methods
Twenty-nine patients with essential hypertension of moderately severe vascular disease, who were evaluated completely to exclude secondary forms of hypertension and to assess involvement of target organs, were included in this study. All were informed about the nature of the investigation and signed consent forms approved by our institutional Human Experimentation Committee. These patients either had never received antihypertensive drugs prior to evaluation or had discontinued their medications at least four weeks prior to study. The hemodynamic studies were performed in the morning after an overnight fast without premedication in a quiet, well-lit room using previously reported techniques. In brief, small segments of polyethylene tubing were introduced intravascularly through an antecubital vein and brachial artery up to the shoulder level using the Seldinger technique. This enabled continuous direct recording at normal (25 mm/sec) and rapid (100 mm/sec) paper speeds of arterial and venous pressures simultaneously with the electrocardiogram (lead II). Control (pretreatment) supine determinations (in triplicate) of cardiac output were obtained with 5 mg indocyanine dye followed by a 5 ml saline bolus flush injection; and this was repeated once again during the fifth minute of 50° upright tilt. After inscription of each indicator-dilution curve the withdrawn blood was returned to the patient. These curves were replotted semi-logarithmically to calculate the minute cardiac output. Thus, these hemodynamic measurements permitted calculation of: cardiac index, by dividing cardiac output by body surface area; total peripheral resistance index, by dividing...
mean arterial pressure by cardiac index; and left ventricular ejection rate index, by dividing stroke index by the ejection time. All statistical data were calculated by paired data analysis using the Student’s t-test.

The 29 patients were classified into four groups. Groups I, II, and III were composed of six, six, and three patients, respectively, and received 0.10, 0.25, and 0.35 mg/kg (body weight) bethanidine in single oral doses, respectively. Supine and upright hemodynamic studies were obtained before and one, one and one-half, two, and three hours after administration of the drug. Group IV (14 patients, all men) received a 0.50 mg/kg oral dose; and hemodynamic measurements were obtained before and one, two, and three hours after administration of bethanidine. All of these latter patients had hypertensive retinopathy of grades II or III severity (K-W-B); evidence of ventricular involvement from hypertension,14 and contracted plasma volume.17 Hemodynamic measurements were not obtained after three hours because of our reluctance to produce unnecessary discomfort from inordinately prolonged intravascular investigations. Nevertheless, pressure and heart rate measurements were obtained at frequent intervals after the patient had returned to his ward.

Results

Following the 0.10, 0.25, and 0.35 mg/kg bethanidine doses, there were no significant changes in arterial pressure or other hemodynamic functions in either the supine or upright tilt positions. Only following the 0.50 mg/kg dose did significant hemodynamic changes occur. Of the 14 patients who received the 0.50 mg/kg dose, eight responded with a fall in supine mean arterial pressure within two to three hours; five patients demonstrated a slight increase in pressure; and one showed no change (fig. 1). The fall in mean arterial pressure in the eight patients averaged 13 mm Hg (126 to 113 mm Hg, P < 0.005, table 1). This hypotensive response was associated with either a reduced cardiac output and/or total peripheral resistance. However, all 14 patients exhibited significant orthostatic hypotension two to three hours after receiving the drug (fig. 2, left panel). Thus, prior to bethanidine mean arterial pressure of the group had increased by 4 mm Hg during upright tilt; but by three hours the drug produced a 19 mm Hg fall in pressure (P < 0.001). This orthostatic hypotensive response was associated with reflexive tachycardia which was not abolished by the drug (P < 0.001 and P < 0.005, before and after treatment, respectively). Cardiac index was significantly reduced during upright tilt (P < 0.001), and this fall with tilt increased almost twofold after bethanidine, reflecting decreased venous return (fig. 2, right panel). Associated with this postural fall in cardiac output was a reflexive increase in peripheral vascular resistance (P < 0.001), which was significantly attenuated after bethanidine (fig. 2, right panel).

Thus, the reflexive sympathetic adjustments were significantly modified by bethanidine, so that the reflexive increase in total peripheral vascular resistance was significantly reduced (19 to 6%, P < 0.025) and the increase in diastolic pressure during the overshoot phase of the Valsalva maneuver was attenuated (from 42 to 10%, P < 0.001; fig. 3).

Arterial pressure was continuously monitored for one hour after oral administration of bethanidine and no significant changes were observed, thereby providing no evidence to incriminate transient pressure elevations related to postganglionic neuronal release of catecholamines. Thus, average pressures before and 15, 30, 45, and 60 minutes after bethanidine were 186/103, 163/102, 184/104,

Table 1

<table>
<thead>
<tr>
<th>Patient</th>
<th>MAP (mm Hg)</th>
<th>CI (ml/min/m²)</th>
<th>HR (beats/min)</th>
<th>TPRI (mm Hg/ml/min/m²)</th>
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</table>

Abbreviations: C = control; D = final measurements three hours after bethanidine; MAP = mean arterial pressure; CI = cardiac index; HR = heart rate; TPRI = total peripheral resistance index.

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Figure 2

Hemodynamic responses of the patients receiving the 0.50 mg/kg oral dose of bethanidine. Figure 2 (left) presents the mean (± 1 SEM) for the supine (S) and 50-degree upright tilt (T) responses in mean arterial pressure and heart rate. Figure 2 (right) represents those average changes for the group of cardiac and total peripheral resistance indices. The statistical comparisons relate to the differences between the supine and upright tilt measurements.

184/103, and 190/108 mm Hg, respectively. Further, arterial pressure was also obtained frequently for eight hours following the completion of the hemodynamic study. The maximum supine hypotensive effect of the drug was observed four hours after drug administration (133/89 and 109/76 mm Hg for supine and standing positions, respectively), after which pressure began to rise progressively. However, the maximum orthostatic hypotensive effect (106/73 mm Hg) occurred six hours after bethanidine was ingested orally, and this effect of the single dose was still present after eight hours (157/98 and 118/82 mm Hg, respectively, for the supine and standing positions). Indeed, four of these 14 patients demonstrated symptomatic orthostatic hypotension five to six hours after administration of this one dose which demanded that they be rapidly reclined to obviate syncope. One additional patient developed severe abdominal cramps at the end of the hemodynamic study (after three hours) which were followed by diarrhea. No other side effects were reported.

Discussion

The acute hemodynamic effects of bethanidine, a relatively new postganglionic sympatholytic agent, were investigated in 29 patients with essential hypertension who received one of four oral doses of the drug. However, only with the highest dose (0.50 mg/kg) did arterial pressure respond; and this action was rather prompt (within two to three hours), having its peak effect after four hours. This rapidity of action possibly reflects the drug’s nearly complete gastrointestinal absorption.10 Although the mechanism of action of bethanidine is not completely understood, it probably is mediated through inhibition of postganglionic neuronal fibers.6 These findings are supported by our present observation of inhibition of several reflexive sympathetic adjustments including significant suppression of the rise in vascular resistance during upright posture and of the increase in diastolic pressure during the overshoot phase of the Valsalva maneuver. And, in addition to the interference with reflexive sympathetic adjustments of the arterioles, bethanidine also enhanced peripheral pooling of blood by promoting greater venodilation and decreased venous return during upright posture. Arterial pressure was reduced in eight patients in the supine position; and this effect was promoted either through a decrease in cardiac output or peripheral vascular resistance. Thus, these effects of bethanidine closely resemble those produced by guanethidine18, 19 and strongly suggest a postganglionic adrenergic inhibitory effect.

The peak effect of bethanidine was observed approximately four to five hours after its administration, with pressure rising progressively thereafter so that by eight hours supine pressure approximated pretreatment levels, although the orthostatic hypotensive effect remained. Similar observations have been reported by others.5, 7-9, 11-13 Although an initial sympathomimetic effect had been reported following parenteral administration of bethanidine,20 this was not observed following oral administration of the drug while pressure was monitored continuously. Further, these acute hemodynamic studies failed to demonstrate any negative (or positive) inotropic or chronotropic effects of bethanidine upon the heart.

The orthostatic hypotension and diarrhea observed in this study further demonstrate effective inhibition of postganglionic adrenergic function in these patients. Diarrhea has been reported to occur with prolonged bethanidine administration but is said to be less bothersome than with guanethidine.5, 9, 11, 12 The inability to demonstrate failure of ejaculation and per-

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sistent evidence of reflexive cardioacceleration during upright posture most likely are explainable by the acute nature of this study in which the drug was administered only as a single dose; therefore, major pharmacological differences from other postganglionic sympatholytics should not be inferred from these observations. That bethanidine produced significant and prompt hypotensive action in all 14 patients receiving the 0.50 mg/kg dosage, which remitted by eight hours, indicates that this compound, although similar in effect to guanethidine, has definite therapeutic potential in the treatment of hypertension.

Acknowledgment

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