Rapid Control of Hypertension with Oral Bethanidine

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Received: February 28, 1972, accepted: May 2, 1972

Summary. A dosing schedule for the administration of oral bethanidine is described, which achieved optimal cumulative effect in each of 8 patients in 3 days or less. Individual patient dosage titration is necessary, because the required cumulative dose cannot be predicted on the basis of blood pressure, or creatinine clearance. The time course of the blood pressure response after the peak acute hypotensive effect was found to be variable and dependent upon the magnitude of effect and time of day. No blood pressure effect was noted in the recumbent position.

Key words: Bethanidine, guanethidine, hypertension, adrenergic blockade, blood pressure, dose response.

Blood pressure can be satisfactorily controlled in most patients with currently available drugs. However, a clinically applicable method of safely and rapidly reducing the blood pressure to a defined therapeutic end point using the oral route is not well defined. Rapid control of blood pressure is desirable in uncomplicated severe, as well as moderate to severe hypertension presenting the usual complications. Treatment of such patients is best begun during hospitalization. We have investigated the usefulness of bethanidine for rapid control of hypertension in 8 hospitalized patients. Bethanidine is an adrenergic neuronal blocking drug similar to guanethidine pharmacologically [3], but characterized by a more rapid onset and shorter duration of action [9, 10, 13]. The pharmacodynamics of bethanidine facilitate rapid control of blood pressure. We report here a schedule that effectively lowered blood pressure in a small series of patients within a two-day period.

Methods

Eight hypertensive Negro females voluntarily participated in the study, having provided informed consent. Six of the eight patients had electrocardiographic and x-ray evidence of left ventricular hypertrophy, but only one had a clinical history of left ventricular failure, which was compensated at the time of the study. All medication except a thiazide diuretic (trichlormethiazide, 4 mg daily) was withdrawn at least 15 days prior to admission to the Clinical Research Unit in Emory University Hospital. Starting on the day of admission all patients received benztiazide, 50 mg q.d. at 8 a.m. and bethanidine placebo, 1 tablet at 4 h intervals between 8:00 a.m. and 4:00 p.m. During the hospital stay, patients were maintained on a constant sodium (100 mEq/day) diet. Body weight was recorded daily and 24 h urinary excretion of sodium, potassium and creatinine determined. Chest x-ray, electrocardiogram, complete blood count, serum electrolytes, creatinine, BUN, bilirubin, transaminase and plasma electrophoresis were done before, during and after administration of active drug. Blood pressure and pulse rate in the supine and standing (2 min) positions were recorded every two hours from 8:00 a.m. until 10:00 p.m.

The patients remained on bethanidine placebo until daily average recumbent and standing blood pressure became stable for 3 consecutive days. At this point bethanidine was substituted for placebo. The bethanidine was administered in a fixed sequence of 3 doses per day. Each dose was designated by its order in the sequence: first day, 10 mg/dose (doses 1-3); second day, 25 mg/dose (doses 4-6); third day, 50 mg/dose (doses 7-9). The active drug was discontinued when diastolic pressure was reduced to < 80 mmHg in the standing position. The final dose which was administered was designated the effective sequential dose, and identified by its sequential number (Table 3). Placebo was reinstated and the time course of the recovery of the blood pressure to the control level was documented. Each patient's blood pressure returned to a value not significantly different from control after discontinuation of the active drug.

Results

Average systolic and diastolic pressures in the supine and standing positions for the 48 h preceding the administration of bethanidine are presented in Table 1. The blood pressure response was quantified
by determining the difference in time-matched mean pressures measured on the treatment and control days (Table 2). The 95% confidence limit of the control arterial blood pressure as obtained by replicate measurements on 2 control days is presented in Table 1. The following parameters of the time course of the bethanidine effect on blood pressure were measured: time from administration of final dose to peak blood pressure response, time from final dose to 50 percent recovery from peak hypotensive response, and time to last recorded effect in excess of the 95% confidence interval of the control pressure observations (Table 3).

For purposes of presentation the patients were tabulated in order of magnitude of peak decrease in standing blood pressure when compared to the corresponding time on the control days (Table 3). Since the therapeutic objective was the same for all patients, this order corresponded in general with increasing levels of control blood pressure values (Table 1). Differences between the tables are due to the method of quantitating control blood pressure. In Table 1, control was calculated as the average of measurements over the 48 h preceding drug administration.

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Bethanidine was successful in reducing standing blood pressure to the therapeutic objective in each patient. However, the effects on recumbent blood pressure were small, short in duration, and not statistically significant for the group as a whole (Table 1). The effective sequential dose ranged from 4 to 8. Figure 1 presents the relationship between cumulative percent of patients responding and the dosage sequence number. Although the small size of the study population and the undefined pharmacokinetics of bethanidine cumulation preclude a precise formulation of the dose-response relationship, the distribution of responding patients relative to logarithm of effective dose sequence number was gaussian in appearance with the peak at dose number 5. The effective dose was not significantly related to creatinine clearance ($p > 0.5$) or blood pressure elevation ($p > 0.5$), Table 3. For example, the patient showing the least response required a larger dose than the patient showing the largest response. Similarly, the range of blood pressure response to a specific dose (example, No. 5) ranged from 35–120 mm Hg.

The patients were divided into groups on the basis of magnitude of blood pressure response: Group 1, patients 1–4, 35–53 (mean, 42) mm Hg, and Group 2, patients 5–8, 72–120 (mean, 88) mm Hg. In the first group, there was no evidence of a significant blood pressure effect of doses preceding the final effective dose, judging by the normal blood pressure at the time of administration of the effective dose (Table 2, Fig. 2). However, a definite within patient dose-related effect was evident in Group 2. The change in blood pressure at time 0 was $38 \pm 12$ (SE) mm Hg, a value quite close to the average maximum effect of Group 1. The subsequent dose in the group resulted in a doubling of blood pressure response indicating that the dose-response relationship is quite steep once an initial response has been produced.

The time of peak effect of bethanidine was relatively uniform, with 80% of the peak occurring in 4 h or less in each case. The subsequent time course of the hypotensive effect was characterized by four features: