Session 12

Guanfacine Alone and in Combination Therapy in the Treatment of Moderate and Severe Hypertension

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This study of guanfacine in 27 patients suffering from moderate-to-severe hypertension showed a satisfactory blood pressure control in 26 patients. Twenty-one of the 27 patients completed a one-year clinical trial with good blood pressure response. The new drugs, acting through the stimulation of the central α-adrenoceptors, are useful in patients suffering from moderate-to-severe hypertension. They are a good alternative to adrenergic neuron-blocking drugs, methyldopa, or β-blockers, and useful in patients with refractory hypertension where conventional therapy has failed.

Physicians are persistently inundated with information introducing new hypotensive drugs, and it is often difficult to complete a critical assessment of a drug before it is replaced or regarded as redundant. With this in mind, it was desirable to do a long-term study of guanfacine (BS 100–141). Guanfacine hydrochloride is one of the most active members of a new class of antihypertensive phenylacylguanidines, with a chemical name as N-amindino-(2,6-dichlorphenyl) acetamide hydrochloride. It appears to produce its therapeutic effects as a result of α-adrenoceptor stimulation at central sympathetic control systems. On the basis of its mechanism of action, guanfacine may be classified with such centrally acting antihypertensive agents as clonidine and guanabenz.

**MATERIAL AND METHODS**

Twenty-one of the 27 patients suffering from moderate to severe hypertension completed a one-year clinical trial with guanfacine. Details of this study have been published previously. The design of the study is shown in Figure 1. Nineteen patients were given guanfacine and a thiazide diuretic; four patients guanfacine alone; three patients with guanfacine, a thiazide diuretic, at times a β-adrenoceptor blocker (pindolol), and during some time a vasodilator (hydralazine). Eighteen patients taking guanfacine with thiazide diuretic and three patients taking guanfacine alone completed the first-year study.

**RESULTS**

The blood pressure therapy with guanfacine in mm Hg was 164 ± 19 systolic/180 ± 10 diastolic; at the end of guanfacine therapy, it was 125 ± 14 systolic/96 ± 7.4 diastolic; and after withdrawal of guanfacine at the end of the first year it was 166 ± 35 systolic/122 ± 14.3 diastolic. In 26 patients a good blood pressure response was achieved. Twenty-five patients reported on occasion 53 side effects, mainly dryness of the mouth (22) and drowsiness (17) from the guanfacine. These side effects almost disappeared at the end of three months of therapy. Details of these results have been published previously.

**DISCUSSION**

The antihypertensive action of guanfacine has been fully confirmed in a series of controlled clinical trials involving more than 1,000 patients and extending for up to two years. Guanfacine is characterized by a comparatively long duration of action due to its relatively long half-life of elimination. This accounts for optimum results being obtained when it is given in a single, undivided daily dose averaging 2 mg. With this type of dosage side effects are kept to a minimum. Guan-

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**Figure 1.** Design of guanfacine (BS 100-141) study.
facine appears suitable for combined drug therapy, and so far no incompatibility with other drugs has been observed.¹

This study with guanfacine showed that it was a useful drug in the treatment of moderate-to-severe hypertension. Side effects consisting of dryness of the mouth and drowsiness usually disappeared within three months after the introduction of guanfacine. Tolerance on a long-term basis was not a problem.

In conclusion the newer drugs acting on the central α-adrenoceptors are a useful alternative to adrenergic-neuron-blocking drugs in the treatment of hypertension. They may also be used as an alternative to methyldopa or β-blockers. In such circumstances the agents acting through the central α-adrenoceptors should be combined with a diuretic to reduce their side effects and dosage. These agents may be of value in refractory hypertension where conventional therapy has failed.

REFERENCES

Use of Oral Clonidine for Rapid Titration of Blood Pressure in Severe Hypertension*

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In 20 patients with severe hypertension, rapid oral clonidine titration was employed for control of blood pressure, with 0.2 mg as the initial dose followed by 0.2 or 0.1 mg at one hour and then 0.1 mg/hour, for a total dose of 0.8 mg. All 20 patients had a successful response, defined as a decrease in mean arterial pressure (MAP) of 30 mm Hg or more or attainment of a diastolic pressure of 100 mm Hg or lower. Baseline MAP was 160 ± 4 (SEM) mm Hg (212 ± 7/334 ± 3) and decreased to 120 ± 3 mm Hg (151 ± 5/104 ± 3). The mean dose was 0.32 ± 0.02 mg, and mean response time 1.8 ± 0.2 hours. Side effects were minimal, except for one patient who died of a cerebral infarct, which developed after the blood pressure was lowered with clonidine. Eighteen patients were treated in our emergency room; 14 were sent home after rapid titration. In ten who returned for a follow-up visit three to seven days later, blood pressure was reasonably well controlled, with clonidine and a diuretic only. Rapid oral clonidine titration can be effectively and, for the most part, safely used for treating severe hypertension even in an ambulatory setting. As with any other hypotensive drug, we recommend proceeding with caution, particularly in patients with symptomatic arteriosclerotic disease.

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Malignant hypertension usually requires immediate therapeutic intervention with parenteral medications such as nitroprusside to prevent potentially irreversible damage to vital organs.¹ More commonly, patients have severe hypertension associated with end-organ damage and have a less serious immediate prognosis, but nevertheless require relatively rapid reduction in blood pressure. In these patients several orally administered antihypertensive agents have been used for rapid blood pressure control.

Single large oral doses of prazosin and labetalol, an agent with combined β-and α-receptor blocking activity, have been successfully used for rapid control of serious hypertension in hospitalized patients.¹² Minoxidil, given in conventional oral doses every four hours, has been utilized successfully to control blood pressure within 24 hours, even in malignant hypertension.¹³ The pharmacokinetic properties of orally administered clonidine¹⁴ have also allowed for its successful use in the control of severe hypertension when given at hourly intervals.¹⁵ In these studies success was measured by a reduction of the diastolic pressure only, and all patients were either in the hospital or hospitalized for a minimum of 48 hours after the acute drug administration. To further explore the efficacy and safety of hourly administration of clonidine and to assess its applicability to an outpatient setting, we examined the use of this drug primarily in patients presenting to our emergency room with severe hypertension and evidence of end-organ damage. We used the mean arterial pressure (MAP) and the diastolic pressure for assessing entrance into the study and success of therapy, and, whenever possible, we sent patients home without hospitalization to be seen again within one week.

METHODS

Twenty adult patients with an initial MAP of 130 mm Hg or greater and an initial diastolic blood pressure of 115 mm Hg or greater were included in the study. Seventeen of the 20 patients (85 percent) had a MAP of 145 mm Hg or greater, and ten (50 percent) had a diastolic pressure of 130 mm Hg or greater. All had evidence of significant end-organ damage (retinopathy, cardiovascular, or renal). Eighteen of the 20 patients were first seen in the Brookdale Hospital Medical Center's emergency room, with the remaining two patients seen in the hospital, previously admitted for problems unrelated to hypertension per se. After a two-hour observation period, during which the blood pressure was checked frequently, the seated baseline blood pressure was established by averaging three recordings taken two minutes apart. During this time a thorough history and physical examination were performed, and patients with papilledema, evidence of hypertensive encephalopathy, congestive heart failure, recent myocardial infarction, stroke, or liver disease were excluded from the study. Informed consent was then obtained from each subject in accordance with standard guidelines approved by the Human Research Committee of the hospital. At 0 time, 0.2 mg of clonidine was given orally. Blood pressure and pulse rate were then recorded in the sitting position every 15 minutes for the first hour and then every 30 minutes for the duration of the acute titration. If the MAP decreased 10 mm Hg or greater and was less than 160 mm Hg at one hour, additional doses of 0.1 mg were given each hour until a successful titration was achieved, defined as a decrease in MAP of 30 mm Hg or more or attainment of a diastolic pressure of 100 mm Hg or less, or until a total dose of 0.8 mg of clonidine was given (maximum seven hours of titration). If, at the end of the first hour, the MAP was 160 mm Hg or greater, or if the decrease in MAP was less than 10 mm Hg and the diastolic pressure was 120 mm Hg or greater, 0.2 mg of clonidine was given followed by 0.1 mg every hour until a