Prazosin Depression of Baroreflex Function in Hypertensive Man

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Summary. Prazosin is a post synaptic alpha adrenergic blocker effective in hypertension, whose hypotensive effect is unaccompanied by reflex tachycardia or hyperreninemia, nor by other evidence of increased sympathetic activity. We studied the baroreceptor reflex arc as a potential mediator of these effects. Twenty-two essential hypertensive men were treated with prazosin alone versus placebo, and experienced a blood pressure fall (from 114.8 ± 3.6 down to 101.1 ± 2.5 mmHg, p < 0.005) unaccompanied by any change in heart rate, plasma renin activity, or several other indices of sympathetic nervous system activity (plasma dopamine-beta-hydroxylase activity; urinary excretion of free catecholamines and vanillyl mandelic acid; all p > 0.1). Concomitant with the blood pressure fall, there was a significant depression of baroreflex arc sensitivity, from 11.4 ± 2.0 ms/mmHg down to 6.6 ± 1.9 ms/mmHg (p < 0.05), without an associated change in cardiac vagal inhibition (291.2 ± 46.2 versus 300.3 ± 19.2 ms, p > 0.1). Baroreflex arc sensitivity depression may in part explain the lack of reflex sympathetic outflow noted during prazosin treatment of hypertension.

Key words: prazosin, baroreflexes, hypertension; reflex tachycardia, alpha adrenergic blockade, dopamine-beta-hydroxylase

Prazosin hydrochloride is a new antihypertensive agent effective in mild to moderate arterial hypertension [1, 2]. The drug is a vasodilator whose mode of action appears to be post synaptic alpha adrenergic blockade [3–7] with consequent relaxation of resistance as well as capacitance vessels.

Unlike other vasodilator agents, such as minoxidil and hydralazine, and nonspecific (pre and post synaptic) alpha blockers, such as phenoxybenzamine, prazosin does not result in reflex activation of the sympathetic nervous system with tachycardia and hyperreninemia [1, 2, 7–11]. In fact, effective antihypertensive therapy with prazosin characteristically occurs without change in heart rate [1, 7, 9, 10] and with unchanged or even suppressed plasma renin activity [1, 8, 9, 11]. Explanations for these phenomena have included the selective post synaptic (vascular, α1) alpha blocking action of prazosin [7] as well as the possibility that prazosin may enhance the cardiac slowing action of acetylcholine by elevating tissue levels of cyclic guanosine monophosphate (GMP) at cholinergic receptor sites in the heart [12].

Another potential explanation for these phenomena exists, however. Both the reflex tachycardia [13, 14] and the hyperreninemia [15–17] seen with vasodilator induced hypotension are thought to be mediated in part by the baroreceptor reflex arc [18]. That is, a diminution in arterial pressure is sensed by the baroreceptors in the carotid sinuses and aortic arch (the afferent limb of the arc) and processed by the central component of the arc in the medulla oblongata, with a consequent increase in effenter limb sympathetic activity, resulting in tachycardia and renin release [19]. Suppression of baroreflex arc function, then, could blunt the expected tachycardia and renin release.

We investigated this possibility in prazosin-treated essential hypertensive man by assessing quantitatively baroreflex arc function [20] as the degree of cardiodeceleration in response to acute phenylephrine-induced hypertension. Efferent sympathetic nervous system activity was assessed biochemically by measurement of plasma dopamine-beta-hydroxylase activity, a proposed index of long-term changes in sympathetic nervous system activity in man [21] and by the 24-h urinary excretion of free catecholamines and vanillylmandelic acid [22].
To explore cholinergic participation in heart rate control, we also quantitated cardiac vagal inhibition, that is, the heart rate change in response to total cholinergic blockade with intravenous atropine [23–26].

We recorded all these measurements, along with blood pressure, heart rate, and plasma renin activity data, in a series of essential hypertensive patients, both during placebo phase and during successful chronic antihypertensive therapy with prazosin alone, in an attempt to isolate prazosin effects upon baroreflex function as well as both sympathetic and parasympathetic nervous activity in the cardiovascular system.

**Patients and Methods**

**Subjects**

We studied 22 male adults with uncomplicated essential hypertension. The average age of the group was (mean ± SEM) 48.4 ± 2.1 years, with a range of 28 to 60 years. Prior to entry into the study, all subjects had mean arterial pressures (MAP), defined as the diastolic blood pressures plus 1/3 of the pulse pressure, of at least 105 mmHg measured in the outpatient clinic.

We attempted to exclude secondary causes for hypertension by history and physical examination; chest roentgenogram; electrocardiogram; intravenous urogram; urinalysis and culture; hemogram; and the 24-h urinary excretion of 17 hydroxy corticosteroids, catecholamines and vanillylmandelic acid.

All subjects were found to be essential hypertensives. Subjects with evidence of end organ damage from hypertension (e.g., congestive heart failure, myocardial infarction, nephrosclerosis, stroke) were excluded.

**Procedures**

In random order, each subject was placed either on oral placebo for one month, or on oral prazosin alone in divided doses for one month, at a dosage individually titrated to reduce mean arterial pressure to less than 105 mmHg. The dose range was 6 to 30 mg daily, with a mean of 12.7 ± 2.8 mg/day. No other medications were utilized, and the diet was unrestricted in fluid and sodium. Each subject completed both the placebo and the prazosin phase of this study; hence, each acted as his own control.

At the end of each one month period, each subject was admitted for 48 h to the Special Diagnostic and Treatment Unit of the San Diego Veterans Administration Medical Center, for a protocol of the following studies.

All subjects gave their informed written consent, and the protocol was approved by the Committee on Activities/Investigations Involving Human Subjects of the University of California, San Diego.

**Measurements**

**Blood Pressure and Pulse:** Mean arterial pressure, by a manual sphygmomanometer, and pulse rate, by palpation, were determined in triplicate upon each hospital admission, and the results averaged.

**Biochemical Studies:** During the first 24 h of hospitalization, urine was collected in an acidified opaque container and stored at 4 °C. The 24-h volume was measured and aliquots were obtained for measurement of free catecholamines and vanillylmandelic acid. In the morning, in the supine fasting state, blood was drawn into chilled heparin tubes for measurement of plasma dopamine-β-hydroxylase activity, and into chilled EDTA tubes for measurement of plasma renin activity. The samples were kept on ice (<30 min) before centrifugation and plasma removal, whereupon the plasma was frozen at −30 °C for future assay. Similar plasma samples for dopamine-β-hydroxylase and plasma renin activities were obtained after 4 h of upright ambulation.

**Blood Volume Studies:** In the morning, supine fasting whole blood volume was measured using sequentially both 51Cr-labelled autologous erythrocytes and 125I labelled serum albumin. Subjects were injected with the isotopes and whole blood and plasma samples were obtained 10 and 20 min later for counting in the Volemetron apparatus. Whole blood volume was determined by combining the results from the chromium measurement (for red cell mass) and the albumin measurement (for plasma volume).

**Hemodynamic Studies:** In the afternoon of the second hospital day, the following hemodynamic studies were performed on 11 patients1, in the recumbent position, measuring brachial arterial pressure directly via an 18 gauge intrarterial cannula connected to a Hewlett-Packard Model 1280-C pressure transducer. Arterial pressure and lead V2 of the electrocardiogram were recorded simultaneously on a two channel Hewlett-Packard Model 7707-B hot stylus recorder at 25 mm/s paper speed. In this fashion, beat to beat variations in both arterial pressure and heart rate could be analyzed and correlated. The following specific studies were undertaken:

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1 (mean age, 49.5 ± 3.1 years)