Blood Pressure and Prolactin: Effects of Guanfacine

Three-Year Follow-Up Study

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SUMMARY Serum prolactin was measured in 76 patients with essential hypertension: 47.4% had elevated serum prolactin, and those with organ damage had presented higher prolactin than those with Phase I (WHO) hypertension. The effect of prolonged treatment (3 years) with guanfacine, an alpha-adrenoceptor stimulant drug, on blood pressure levels, heart rate, and prolactin was evaluated in 15 patients with moderate essential hypertension (WHO: Phase II) and hyperprolactinemia. Treatment produced a marked reduction in blood pressure levels and heart rate. Guanfacine decreased serum prolactin significantly (p < 0.001), and the inhibition persisted during the 3-year follow-up. The daily dosage of guanfacine did not have to be changed during the 3 years of treatment. Side effects of guanfacine were only observed during the first 3-4 months of therapy. The hypotensive effect of guanfacine was increased by the administration of a diuretic, a vasodilator, or a beta-adrenergic blocking drug. The results indicate that guanfacine administered alone or in combination is an effective drug for treatment of patients with essential hypertension. The inhibitory effect of guanfacine on prolactin suggests that hypothalamic or extrahypothalamic adrenergic pathways may participate in the regulation of prolactin secretion. (Hypertension 3 (suppl II): 11-222-11-225, 1981)

KEY WORDS • hypertension • hypertension treatment • alpha adrenergic central receptors • diuretics • alpha-adrenergic drugs • vasodilators

It is now recognized that dopamine inhibits prolactin secretion in man and animals. The inhibitory effect of norepinephrine on prolactin secretion is less known, since contradictory results of studies performed in vivo and in vitro have been reported during recent years.1 Guanfacine (Estulic, Sandoz) (BS 100-141: N-amidino-2- (2,6 dichlorophenyl) acetamide hydrochloride) is a new antihypertensive agent that is thought to reduce blood pressure levels by stimulation of the alpha receptors in the central nervous system, thereby reducing central sympathetic outflow and plasma noradrenaline concentration.2 Its pharmacological action is similar to that of the imidazoline derivative, clonidine, which causes a decrease in the activity of the peripheral sympathetic nervous system mediated by way of central α-adrenoreceptors.3 Guanfacine, unlike clonidine, does not inhibit dopamine turnover and is ineffective when locally applied to the medulla oblongata.4 Since recent studies have indicated that patients with essential hypertension present elevated serum prolactin levels,4 it is of interest to evaluate the effect of long-term treatment with guanfacine on serum prolactin in patients with essential hypertension.

Material and Methods

Serum prolactin levels were measured in 76 patients with essential hypertension: 32 women and 44 men, aged 32 to 72 years old. The patients had a complete clinical examination that confirmed the diagnosis of essential hypertension, the absence of other diseases, and hypertension Phase IV (World Health Organization (WHO). The patients were classified according to WHO phases of arterial hypertension; diastolic blood pressure level (DBP); coronary risk score (Duncan and Best),5 and eye-ground examination (Keith-Wagener classification).

For long-term treatment we selected 15 patients (9 women and 6 men) aged 32 to 62 years old with established moderate essential hypertension (Phase II according to WHO, with a diastolic blood pressure of 105 and 120 mm Hg, ocular fundi Phase II or III, and a high prolactin level of 25.4 ± 5.4 ng/ml). After a washout period (2-3 weeks) during which the patients were given a placebo, blood pressure levels and heart
rate in the lying (15 min) and standing (2 min) positions were determined several times. Guanfacine 1 mg daily at bedtime was given, and the dosage was progressively increased (once a week) until a satisfactory therapeutic effect was obtained (a blood pressure less than 160/90 mm Hg); mean daily dose was 2 mg. Blood pressure levels (DBP-phase 5 Korotkoff sounds) and heart rate were measured every second week at the beginning of treatment and thereafter at monthly intervals. Serum prolactin was measured during the last week of placebo treatment and during administration of guanfacine at 3, 6, and 12 months of treatment. During the last 2 years of therapy, the measurements were performed in all patients at the same time of the year, in Winter (July) and Summer (February), since Lakatua et al. have demonstrated marked interpopulation differences in the circadian rhythm of prolactin during different times of the year.

Finally, in the groups of patients with moderate and severe hypertension who had responded poorly to guanfacine alone (4 mg/day) for 1 month, the combination of guanfacine (2 mg daily) with a β-adrenoceptor-blocker, pindolol (Visken, Sandoz, 15 mg/d); a diuretic, chlortalidone (Hygroton, Ciba-Geigy 50 mg/day); or a vasodilator, BQ 22-708 (En- dralazine, Sandoz 30 mg/d) was given. Serum prolactin was measured during the last week of placebo treatment, the last week of guanfacine treatment, and after receiving combined treatment during 2 months. In addition, serum prolactin levels were measured in 26 normal subjects (14 men and 12 women, aged 29 to 69 years old) under the same experimental conditions in summer (February, 1978). Each serum sample was assayed for prolactin in duplicate utilizing the radioimmunoassay kit provided by CEA-IRESORIN (Sallugia, Vercelli, Italy).* Results are expressed as means ± DS ng/ml and were analyzed by the Student's t test.

Results

Serum prolactin levels in patients with essential hypertension (20.0 ± 7.3 ng/ml) were significantly higher (p < 0.001) than in normal subjects (11.4 ± 4.8 ng/ml); the highest normal value was 20.1 ng/ml. Based on this level, 47.4% of patients with essential hypertension presented high serum prolactin levels (fig. 1). No significant difference in serum prolactin levels was observed between males and females, nor between subjects older than (21.9 ± 7.7 ng/ml) or younger than (18.1 ± 8.1 ng/ml) 45 years of age.

Patients with essential hypertension in WHO Phase III presented significantly higher (p < 0.001) serum prolactin levels (29.4 ± 5.8 ng/ml) than patients in WHO Phase I (8.2 ± 4.5 ng/ml) (fig. 2). However, no correlation between serum prolactin and DBP levels could be demonstrated (diastolic blood pressure less than 115 mm Hg: 19.2 ± 8.2 ng/ml, diastolic blood pressure greater than 115 mm Hg: 18.1 ± 9.7 ng/ml). Serum prolactin was also significantly higher in patients with Grade III fundal changes than in patients with normal eye grounds (p < 0.001) (fig. 3). In addition, patients in whom the coronary risk score was high presented higher levels of serum prolactin than patients with a low score (fig. 4).

Treatment with guanfacine produced a marked drop (p < 0.001) in serum prolactin (from 25.4 ± 5.4 to 9.2 ± 4 ng/ml at 6 months), which persisted during the 3-year follow-up: at 1 year, 12.3 ± 3.7 ng/ml; at 2 years 9.7 ± 4.8 ng/ml; and 3 years, 11.3 ± 3.1 ng/ml. No seasonal changes in prolactin levels were observed.

*The radioimmunoassay for measurement of serum prolactin was performed in 50 μl serum samples using iodine-125-labelled prolactin (maximum specific activity, 100 μCi/μg at pH 7.4, phosphate buffer) The separation was made by the method of double antibody, the second antibody being fixed on cellulose (immunosorbent). Standard range 5-200 ng/ml Sensitivity 5 ng/ml (at the 95 B/Bo level) Specificity percent cross-reactivity prolactin 100%, HGH. 0.24%, HPL, LH, FSH, and TSH 0.001%. Average recovery 98.5%. Intrassay coefficient of variation for the three different dilutions was 6.6%; coefficient of variation of a pooled sample of plasma measured with each run was 5.3%, and the percent maximum bound (MB) count as a measure of the reagents' functionality and operating conditions during the course of the assay ± 7% between runs. Correlation with international standard. 1 mg NIH — VLS 2 = 30.40 U I MRC 75/50 H.
and there was no correlation between the decrease in prolactin and response to treatment (serum prolactin levels in poor responsive patients decreased from 23.7 ± 6.1 to 14.5 ± 5.4 ng/ml). The combined treatment with guanfacine and a diuretic (12.7 ± 4.0 ng/ml), a beta-blocker (pindolol) (15.1 ± 5.7 ng/ml), or a vasodilator (17.1 ± 6.0 ng/ml) did not modify serum prolactin.

Statistical evaluation of the 15 patients treated with only guanfacine showed that the decrease in blood pressure was highly significant in all instances (p < 0.001). The decrease in mean arterial pressure (MAP) varied between 19% and 29%. The heart rate was particularly reduced in patients presenting initial tachycardia; on the average it was lowered about 10%. The antihypertensive effect of guanfacine did not change during the 3 years of treatment and there were no significant changes in body weight or in heart rate. Detailed analysis of the patients' sex, age, initial diastolic blood pressure, and body weight showed no correlation with any of these characteristics and the daily dose of guanfacine administered. The most common side effects were dryness of the mouth (100%) and constipation (80%), Fatigue (30%), sedation (20%), and muscular weakness (15%) were encountered less frequently. During the course of treatment all side effects decreased and finally disappeared during the third to fourth month of therapy. No impairment of hematological or biochemical values that could be attributed to the drug were found. Administration of the combination of guanfacine with other antihypertensive drugs improved BP control. Addition of the diuretic or pindolol did not modify the heart rate but combined treatment with a vasodilator produced a rise in heart rate (74 ± 8 to 86 ± 9 beats/min).

**Discussion**

When different populations of the world were tested for variability in serum prolactin levels, as well as, in other hormones, chronoepidemiological differences were observed.8 The results compared herein were all based on determinations performed in a single laboratory in samples drawn at the same time of the day and same time of the year during the initial study and during the 3 years of treatment, to exclude circadian and circannual variations of prolactin secretion as a possible cause of differences in hormone levels.
As previously demonstrated, the present data showed that nearly half of the patients with essential hypertension presented high prolactin levels. Furthermore, in patients with organ damage due to arterial hypertension, serum prolactin was higher than that in patients with essential hypertension in WHO Phase I and with normal fundus findings. In addition, no correlation was found between the hypertensive effect of the drug and the inhibitory effect on prolactin. Thus, these results suggest that it is unlikely that prolactin may play a role in the development of essential hypertension. On the contrary, the rise in prolactin levels may represent a late event in the natural history of essential hypertension. It can be speculated that the measurement of progressively higher serum prolactin in patients with essential hypertension could perhaps indicate a progressive deterioration of the cardiovascular system. In support of this theory, the present study demonstrates a correlation between the coronary risk score (Duncan-Best) and serum prolactin levels. Since, on one hand, it was recently reported that patients who had suffered cardiovascular accidents had higher serum prolactin levels than patients free of these events, and, on the other hand, experimental data have indicated that pretreatment with prolactin increases the pressor response to the administration of vasoactive peptides, it is possible that prolactin may play a role in the development of cardiovascular complications in patients with essential hypertension.

Our previous studies have demonstrated that guanfacine treatment during 1 to 6 weeks significantly decreases serum prolactin in patients with essential hypertension, presenting hyperprolactinemia. This paper confirms the sustained inhibitory effect of guanfacine on serum prolactin in this group of patients. Other investigators have reported that a single oral dose of guanfacine could decrease prolactin secretion in postpartum women significantly and that short-term treatment could also inhibit the insulin-induced prolactin rise. In contrast, normal volunteers showed no effect of guanfacine on the resting levels of prolactin, nor on prolactin release by metoclopramide.

In man and in animals, the main control of prolactin secretion is inhibitory, and it has been indicated that dopamine is the physiological inhibitor of prolactin secretion. In addition, recent experiments suggest that norepinephrine may also have an inhibitory action on prolactin secretion. The mechanism by which guanfacine affects prolactin secretion is not clear. Since the drug does not modify normal serum prolactin levels, it can be speculated that the hypothalamic or extrahypothalamic norepinephrine pathways that control prolactin secretion may be an alternate mechanism in the regulation of prolactin secretion.

It is evident, however, that the availability of this new alpha-adrenoceptor agonist offers an excellent opportunity to investigate further the adrenergic mechanism that regulates prolactin secretion in man and animals, especially its effects on patients with essential hypertension presenting normal serum prolactin levels. To test the possible importance of prolactin in the development of cardiovascular complications, further long-term studies should be performed to determine the incidence of cardiovascular accidents in patients treated with guanfacine or with other antihypertensive drugs that decrease serum prolactin levels.

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