Eur Arch Psychiatry Clin Neurosci (1991) 241:77–81

European Archives of Psychiatry and Clinical Neuroscience

Hormonal Responses to Clonidine and Urinary MHPG in Delusional and Nondelusional Melancholic Patients: a Placebo-Controlled Study

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Received August 15, 1990

Summary. The growth hormone (GH) and cortisol responses to intravenous clonidine (0.15 mg) treatment of 25 melancholic patients, 12 with and 13 without delusions, were studied with placebo control. The baseline concentrations of the main noradrenaline metabolite, 3-methoxy-4-hydroxyphenylglycol (MHPG) were also estimated in urine. Cortisol plasma levels decreased significantly and equally after both placebo and clonidine. Baseline cortisol levels correlated positively with urinary MHPG. Clonidine did not increase GH levels significantly over time compared with placebo. Delusional melancholic patients tended to have smaller GH responses to clonidine than nondelusionals ($F = 2.18$, $P = 0.06$). There were no differences in GH response to clonidine between high and low MHPG excretors.

Key words: Growth hormone – Clonidine – 3-Methoxy-4-hydroxyphenylglycol – Melancholia – Delusions

Introduction

The differences in treatment response between delusional and nondelusional unipolar depression raises the question whether the former group represents a distinct subtype of major depression. Several studies have compared symptoms, demographic data, family history and biological variables (see Roose and Glassman 1988 for review). More positive have been the findings of biological studies. Two publications reported that delusional depressives have higher cerebrospinal fluid homovanillic acid compared with nondelusional depressives (Sweeney et al. 1978; Aberg-Wistedt et al. 1985). Also, patients with delusional depression have been reported to be more likely to have higher plasma cortisol levels after dexamethasone and higher rates of abnormal dexamethasone suppression that nondelusional depressives (Roose and Glassman 1988).

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Clonidine, a specific α_2-adrenergic receptor agonist, increases growth hormone (GH) secretion in man (Lal et al. 1975; Checkley 1980). Several studies have demonstrated a reduced response of GH to clonidine in depressed patients, particularly in endogenous depression, compared with normal controls (Matussek et al. 1980; Checkley et al. 1981; Charney et al. 1982). This finding has been considered to suggest abnormal neuroendocrine function in depression, and in particular, the possibility of diminished post-synaptic α_2-receptor sensitivity at least in subpopulations of depressed patients.

In a previous study, we found elevated urinary 3-methoxy-4-hydroxyphenylglycol (MHPG) levels in delusional depressed patients as compared with nondelusional patients. Higher MHPG levels reflect increased noradrenergic activity, which may be associated with decreased α-adrenegic receptor responsiveness. Thus, differences in α_2-adrenergic receptor sensitivity between delusional and nondelusional depressed patients can be expected.

To test this possibility, we studied the GH and cortisol responses to clonidine and to placebo in 25 melancholic patients, 12 with and 13 without delusions, mood congruent. The design included measurements of the main noradrenaline (NA) metabolite MHPG in urine, as an index of noradrenergic activity.

Patients and Methods

All patients were hospitalized in the Psychiatric Clinic of the Athens University Medical School, Eginition Hospital. We evaluated 25 patients (13 male, 12 female) with a mean age of 53.0 years (SD = 10.2, range 32–65 years). Diagnosis was made by two psychiatrists independently, on the basis of standard clinical interviews after 10 days of adaptation in the ward. All patients suffered from unipolar depression and met DSM-III criteria (1980) for major depressive episodes with melancholia including 12 with psychotic features, mood congruent, and 13 without psychotic features. Seven women were menopausal and the other 5 were normally menstruating. In the latter cases estimations were made in the preovulatory phase of the cycle. Of the 7 menopausal women 3 were nondelusional and 4 delusional. The mean weight of nondelusional depressives was 73.8 kg (SD = 5.4, range 68–80 kg), and of delusional depressives 71.3 kg (SD = 4.2, range 66–78 kg). The

patients had a minimum score of 20 in the 17-item Hamilton Depression Rating Scale (HDRS) (Hamilton 1960), and a mean HDRS score of 27.9 (SD = 5.6, range 20–40). They had no signs of medical, neurological or endocrinological illness, as checked by physical and laboratory examination. The patients and/or their relatives gave informed consent for participation in the study.

All patients had received antidepressants before entering the study. They were free of antidepressants for at least 3 weeks before starting the trial. Antidepressant medication was gradually withdrawn and replaced by 30 mg/day prazepam, which was given to all 25 patients during the whole trial.

Twenty-two subjects were studied with both intravenous clonidine hydrochloride (0.15 mg in 10 ml saline) and saline (10 ml) on different days, and 3 subjects received only clonidine. On the first test day, all patients received placebo infusion and the next day clonidine.

After an overnight fast, at 8.00 a.m. an intravenous line was inserted into the forearm vein and kept open with heparin solution. The patients were not permitted to sleep during the blood sampling period. Clonidine or placebo was administered at 9.00 a.m. Blood samples were collected at −15, 0, 15, 30, 45, 60, 75 and 90 min from administration of clonidine or placebo. The samples were centrifuged and the plasma stored at −30°C until the day of analysis.

On the first test day, a morning urine specimen was collected for the estimation of MHPG. A morning urine sample was preferred to 24-h collections, because it covers a more homogeneous time period, and allows a strict nursing supervision of urine collection, at least as demonstrated in our clinic, thus diminishing the possibility of missing night voidings. It also minimizes the influence of changes in mood during the day due to external factors, physical activity, or food and drink, all of which may influence the turnover of biogenic amines (Fernstrom 1976; Harris et al. 1985). Patients voided the previous night before going to bed (around 10 p.m.), and all urine samples were collected at the same time in the morning (7.30 a.m.). Some patients used to void once during the night between 2 and 3 a.m. These voidings were also collected. Urine samples were kept at −30°C until analysis.

Blood pressure and pulse rate were recorded throughout the trial. Also, patients' complaints expressing sedation like drowsiness and tiredness were continuously noted.

GH concentrations were measured using the radioimmunoassay kits of Medgenix Diagnostics, Fleurus, Belgium, with an intraassay coefficient of variation of 5% and interassay coefficient of variation of 8% and expressed in nanograms per millilitre of plasma. Cortisol was measured by the radioimmunoassay kit of Diagnostic Systems Laboratories, Webster, Texas, USA, with coefficients of variation around 10% and expressed in nanograms per millilitre of plasma. MHPG was estimated by gas chromatography. The technique includes hydrolysis with glusulase, extraction into ethyl acetate and derivatization with trifluoroacetic anhydride. The derivative is dissolved in dry ethyl acetate and injected into a SE-30 column, in a Perkin-Elmer Sigma-3 gas chromatograph, connected to a Sigma-10 integrator. The concentrations were calculated from the difference in peak area of samples in which known amounts of pure MHPG have been added at the beginning of the procedure. The coefficient of variation was around 10%. GH response to clonidine was calculated using (a) the peak value reached after clonidine injection and (b) the area under the curve (GHAUC) t_0–t_{90}. The calculation of GHAUC was done using a trapezoidal approximation of the total area under the hormone response curve, with time intervals of 15 min.

Statistical analysis included two-way ANOVA, Mann-Whitney U test, Pearson's and Spearman's correlation coefficients. All significance test were taken two-tailed.

Results

The results of two-way ANOVA assessing the effect of clonidine on GH levels for GHAUC (six 15-min inter-

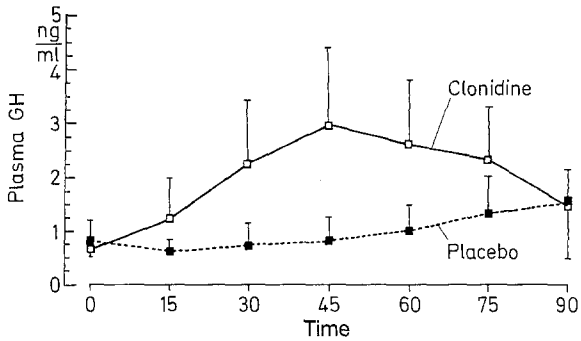
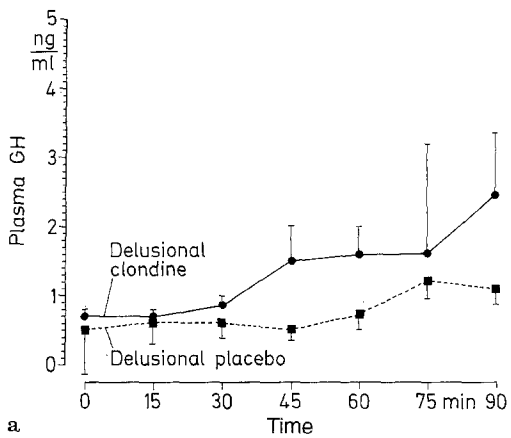


Fig. 1. Plasma growth hormone (GH) levels before and after saline or clonidine injection in melancholic patients (mean, SEM), n = 21. Two-way ANOVA for GHAUC t_0–t_{90}: by time: $F = 1.99$, $df = 20$, $P = 0.08$; by treatment (clonidine vs placebo) $F = 2.04$, $df = 20$, *NS;* interaction $F = 1.76$, $df = 20$, NS



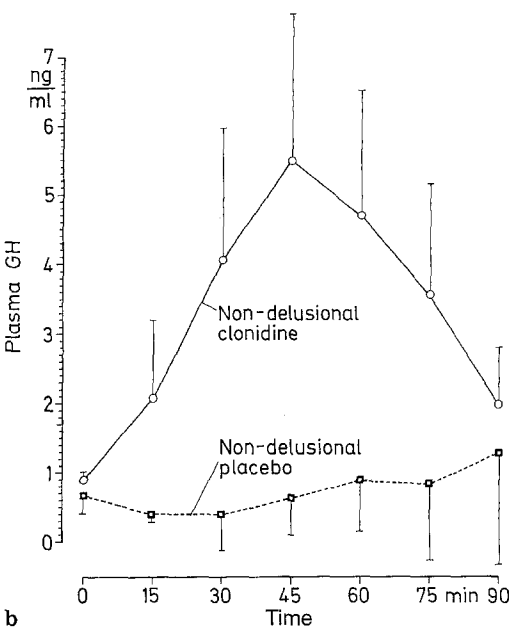


Fig. 2a and b. Plasma growth hormone (GH) levels before and after clonidine injection in delusional (n = 12) and nondelusional (n = 13) melancholic patients. Two-way ANOVA for GHAUC t_0–t_{90}: by time: $F = 1.82$, $df = 24$, NS; by group (delusional vs nondelusional): $F = 3.17$, $df = 24$, $P = 0.085$; interaction: $F = 2.18$, $df = 24$, $P = 0.06$

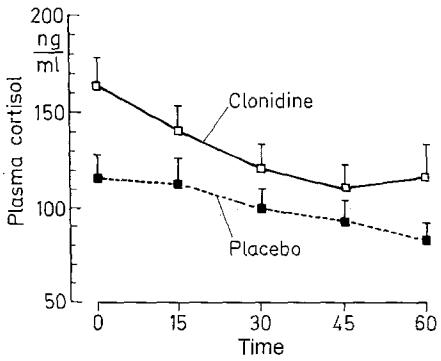


Fig. 3. Plasma cortisol levels before and after saline or clonidine injection in melancholic patients ($n = 21$). Two-way ANOVA: by time: $F = 24.36$, $df = 20$, $P = 0.00001$; by treatment (clonidine vs placebo): $F = 0.48$, $df = 20$, NS; interaction: $F = 1.89$, $df = 20$, NS

vals) are given in Fig. 1. The effect of clonidine vs placebo was not significant ($F = 2.04$). A trend toward a significant response over time was found ($F = 1.99$, $P = 0.08$). The treatment × time interaction which reflects a difference in the magnitude of GH response profiles between clonidine and placebo was not significant ($F = 1.76$).

Delusional and nondelusional melancholic patients did not differ significantly with respect to age, HDRS score, baselines GH levels and urinary MHPG excretion (Mann-Whitney U test), and had a similar male/female ratio (Fisher's exact test). The ANOVA for GHAUC data revealed a trend toward a significant effect of group (i.e. nondelusional vs delusional group, $F = 3.17$, $P = 0.085$), a nonsignificant effect of time ($F = 1.82$, NS) and a trend toward a significant time × group interaction ($F = 2.18$, $P = 0.06$). This means that delusional melancholic tended to have smaller GH responses to clonidine that nondelusionals (Fig. 2). Another ANOVA (diagnosis × peak GH) demonstrated a marginal but significant difference in the peak GH between nondelusional (mean: 5.22 ± 8.33) and delusional subgroups (mean: 0.20 ± 0.30): $F = 4.73$, $P = 0.038$.

Preclonidine plasma cortisol levels were not correlated with age or HDRS score but showed a positive correlation with urinary MHPG excretion which reached significance: $r = 0.44$, $P = 0.050$ (Pearson correlation coefficient).

Two-way ANOVA demonstrated a highly significant overall decrement of cortisol following clonidine administration over time ($F = 24.36$, $P = 0.00001$), a nonsignificant drug difference (clonidine vs placebo) ($F = 0.48$) and a nonsignificant time × drug interaction ($F = 1.89$; Fig. 3). Since clonidine and placebo had a similar effect on cortisol levels, we did not attempt comparisons between delusional and nondelusional melancholic patients with regard to this parameter.

Discussion

Seventeen of our 25 unipolar melancholic patients (68%) had a blunted GH response to clonidine. As shown by ANOVA, no difference with regard to GHAUC emerged between clonidine and placebo administration. One could assume that these findings further support the hypothesis of a subsensitive post-synaptic α_2-receptor function. However, the following issues should be considered. First, it has been demonstrated that melancholic depressives have a significantly lower GH response to clonidine administration compared with those without melancholic features (Amsterdam et al. 1989). In the present study, all depressed patients fulfilled the criteria for DSM-III melancholia, and this may account for their markedly attenuated GH response following clonidine. Second, it has been reported (Matussek et al. 1980) that postmenopausal women, whether normal or depressed, had significantly diminished GH response to clonidine compared with pre-menopausal women. The inclusion of 7 postmenopausal females in our sample may have had a confounding influence on the profoundly blunted hormonal response. A third problem appears to be the previous treatment with antidepressants. Corn et al. (1984) indicated that the blunted GH response to clonidine remained 2 weeks after discontinuation of antidepressants. Schittecatte et al. (1989) observed that a group of depressed patients with major depressive disorder who had never received antidepressant therapy had a normal GH response to clonidine compared with a normal control group. Contrary to this, and compared with the same control subjects, the authors found a markedly blunted response in a group of matched depressed patients who had not received antidepressant drugs for at least 2 weeks. In the present study all 25 patients were unmedicated for the same period (3 weeks). It was thought that this time would be sufficient or at least have the same influence, operating as a nonconfounding factor, on each patient's hormonal responsiveness. A similar methodological issue is the prazepam use during the trial. We could not find reports on the influence of prazepam or other benzodiazepines on GH responses to clonidine. Therefore, a confounding effect on the results cannot be excluded. However, we note that all 25 patients received the same prazepam dose (30 mg). Finally, the clonidine dose could be a matter of discussion. Since all 25 patients received 0.15 mg of clonidine, which corresponds to 2.1 μg/kg, one could argue that the dose was small for the heavier patients. However, none of them was overweight by more than 14%. Therefore, it is not expected that this factor interfered with the results.

The results of the present study failed to show a significant association or even a suggestive trend between increased noradrenergic activity (baseline urinary MHPG) and decreased α_2-receptor responsiveness (GH peak levels) in the entire patient group. Previous investigators have found a negative association between baseline plasma MHPG and average GH peak in both bipolar and unipolar depressed patients (Siever and Uhde 1984).

Without disregarding the considerations mentioned above and the variability in the GH response to clonidine reported in previous studies (Checkley et al. 1984), we compared the 12 delusional and the 13 nondelusional melancholic patients with respect to GHAUC

after clonidine. The former group had smaller GH responses that the latter, but the two-way ANOVA only revealed a trend difference. In contrast to these negative results, GH peak levels were found to be significantly lower in the delusional subgroup. It has been reported that melancholic patients show a more decreased GH response to clonidine that those without melancholia (Amsterdam et al. 1989). In this respect perhaps, we have dealt with a more biologically homogeneous patient group. In other words, the GH response to clonidine was too profound to reveal differences between delusional and nondelusional subgroups. With the trend difference in GHAUC and the marginal although significant difference in GH peak levels, we feel that the noradrenergic receptor responsiveness using clonidine challenge in delusional depressed patients deserves further exploration. In a previous study, we noted a trend for there to be higher urinary MHPG levels in the delusional than in the nondelusional unipolar depressed patients (Lykouras et al. 1988). The present findings showed no meaningful differences in urinary MHPG excretion between the delusional and nondelusional melancholic groups. The presence of melancholia may counteract possible differences, since the mean MHPG levels (10.4) of the 25 patients were closer to the mean MHPG of the delusional rather than to that of the nondelusional group (8.0) of our previous study.

The baseline plasma cortisol levels of melancholic patients decreased significantly following both clonidine and placebo administration but without a significant difference between the two. This is in agreement with previous investigators who administered clonidine 2.0 μg/kg by intravenous infusion (Hoehe et al. 1988) or used 150 μg orally (Hunt et al. 1986) in healthy subjects. The same was demonstrated by Brambilla et al. (1987) in anorectic patients. On the other hand, Matussek et al. (1980) did not find a cortisol response to placebo in contrast to the effect of clonidine in diminishing plasma cortisol concentration. Siever et al. (1984) noted a significant fall in plasma cortisol levels following both clonidine and placebo, but the cortisol decrease was 6 times greater. The decrease in cortisol levels after placebo could be the result of the circadian pattern of cortisol secretion occurring in depressed patients (Sachar et al. 1973), to account for the similar decreases in cortisol levels after placebo and clonidine. Considering the clonidine effect as nonspecific, we did not compare delusional and nondelusional patients for this test.

An interesting finding, although at a trend level, is the positive association between urinary MHPG excretion and baseline plasma cortisol levels in the entire group of our melancholic patients. Previous studies in unipolar depressed patients have shown a positive significant association between (a) plasma cortisol and urinary MHPG (Stokes et al. 1981), (b) plasma cortisol and MHPG levels (Jimerson et al. 1983) and (c) urinary free cortisol and MHPG excretion (Rosenbaum et al. 1983).

A clinical but not significant reduction in pulse rate and systolic blood pressure was observed after clonidine injection. The sedative effect was apparently not marked and appeared within 30 min of receiving clonidine, but it was not present at the end of the trial.

Despite the negative results of the present study, further investigation of noradrenergic activity in the subtype of delusional depression is warranted in a larger group of patients as well as in other clinical subcategories of major depressive illness.

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