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Neuroendocrine effects of quetiapine in healthy volunteers

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Abstract

The present study measured prolactin, cortisol, ACTH and growth hormone in healthy male volunteers following an acute oral administration of quetiapine, an atypical antipsychotic with high affinity for H_1 and moderate affinity for σ , α_1 , 5-HT₂, α_2 and D₂ receptors. Fifteen male volunteers entered this randomized double-blind, cross-over, placebo-controlled study. Blood samples were drawn every 30 min from 09:00 hours to 13:00 hours. The first samples were drawn immediately before the administration of 150 mg quetiapine or placebo. Mean results for each hormone and ANOVA for repeated measures were performed. The area under the curve (AUC) hormonal values were calculated and compared by paired *t* test. The ANOVA showed an increase of prolactin after quetiapine administration from time 60 min up to the end of the observation period. Cortisol decreased after quetiapine administration from time 150 min to time 240 min. ACTH secretion showed no difference compared to placebo. There was a late increase in growth hormone secretion, significant in comparison with placebo only at time 210 min. The AUC values were statistically different for prolactin and cortisol compared to placebo. A single dose of quetiapine (150 mg) increased prolactin secretion probably due to a transiently high D₂ receptor occupancy at the anterior pituitary. Cortisol secretion decreased as was expected from quetiapine's pharmacodynamic profile. The lack of response of ACTH might be, at least in part, explained by the low hormonal assay sensitivity. The late growth hormone increase might have been due to quetiapine's antagonism of H_1 receptors.

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Introduction

Studies of neuroendocrine effects of antipsychotics have been concentrated on prolactin (Prl), with the other hormones playing a secondary role. This is probably due to the role assigned to dopaminergic pathways in the pathophysiological hypotheses of psychosis (Meltzer and Deutsch, 1999). Those studies have shown an increase in Prl secretion, secondary to dopaminergic antagonism at the anterior pituitary and have been conducted in patients and healthy volunteers (Garver, 2000). Hyperprolactinaemia is responsible for many endocrine side-effects of antipsychotics, e.g. decreased libido, galactorrhoea.

In fact the increased Prl secretion seems the most consistent biological marker of the effects of antipsychotics in healthy volunteers among many neuropsychological, neurophysiological, neuroendocrine tests and subjective effects (de Visser et al., 2001). Moreover, the doses of antipsychotics necessary to induce Prl elevation were clearly related to their affinity for D₂ receptors and the recommended initial therapeutic dosage.

Different neuroendocrine effects would be expected from atypical antipsychotics, since they differ from classic antipsychotics on pharmacodynamic profiles. In fact, one of the proposed criteria to distinguish typical from atypical antipsychotics is that the latter do not induce sustained elevations in Prl secretion (Markowitz et al., 1999). The simultaneous antagonism of serotonergic and dopaminergic receptors (5-HT₂/D₂), probably related to its antipsychotic activity, may change the secretion of hormones like growth hormone (GH) and cortisol (Cor) through serotonergic

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pathways. Serotonergic agonists may increase GH and Cor blood levels, whereas antagonists may reduce them, but data are still inconclusive (de Visser et al., 2001).

Quetiapine is a dibenzothiazepine antipsychotic with a t_{\max} of 2 h and a half-life of approx. 7 h. It is an antagonist with high affinity for H_1 histaminergic receptors; moderate affinity for σ (opiate), α_1 and α_2 adrenergic, 5-HT₂ serotonergic and D₂ dopaminergic receptors; low affinity for 5-HT_{1A} serotonergic and D₁ dopaminergic receptors, and practically no affinity for benzodiazepinic binding sites or muscarinic receptors (Caccia, 2000; Green, 1999).

Some studies have demonstrated that quetiapine does not produce sustained elevations of Prl concentrations (Arvanitis et al., 1997; Kapur et al., 2000; King et al., 1998; Small et al., 1997; Wetzal et al., 1995), and some patients even showed a small decrease in Prl levels (Arvanitis et al., 1997).

The low incidence of extrapyramidal side-effects and the lack of a sustained increase in Prl concentrations are explained by quetiapine's low affinity for D₂ receptors coupled with its high affinity for H_1 and 5-HT₂ receptors. In fact, Kapur et al. (2000) investigated the in-vivo effects of quetiapine on D₂ and 5-HT₂ receptors using positron emission tomography, and found a significant occupation of D₂ receptors (58–64%, with [¹¹C]raclopride), 2–3 hours after a single dose of quetiapine followed by a significant decrease to very low levels (0–27%) 12 h later. Their study has also shown that quetiapine does not produce sustained Prl level elevation.

The aim of this study was to assess the hormonal responses [Prl, Cor, adrenocorticotrophic hormone (ACTH) and GH] to an acute single dose of quetiapine in healthy volunteers.

Method

Subjects

Fifteen healthy male volunteers, undergraduate students, age ranging from 18 to 21 yr (mean 20 yr), body mass index (BMI) (mean \pm S.D.) 22.64 ± 2.86 , were included after signing an informed consent. The Ethical Committee of the Federal University of São Paulo had approved the study. Their physical and mental health was evaluated through a structured interview (*Structured Clinical Interview for DSM-IV Axis I Disorders – Non-patient Version*; First et al., 1996), physical examination, laboratory tests (haemogram, Na⁺, K⁺, glucose, serum creatinine, uric acid, aspartate aminotransferase, alanine aminotransferase and

bilirubin) and an electrocardiogram. Abnormal results, history of psychiatric disorders and history of familiar psychiatric disorders (first-degree relatives) were exclusion criteria. None of the volunteers was excluded from the study.

Procedure

Quetiapine (150 mg) and placebo were administered in a double-blind, randomized, cross-over design. The dose of 150 mg was chosen because it is within the clinically effective dose range, although it is higher than the initial dose. Fasting volunteers arrived at 07:30 hours the research centre and at 08:00 hours an i.v. catheter was inserted into an antecubital vein and kept open with heparinized saline (20 ml saline:0.5 ml heparin, 25000 IU/5 ml). Then, they had a low-fat breakfast (from 08:00 to 08:30 hours) and were admitted in the study room, where they remained in bed during the whole experiment. Blood samples were drawn every 30 min from 09:00 to 13:00 hours. The first sample was drawn immediately before the ingestion of 150 mg quetiapine or placebo. One week later, the procedure was repeated. Volunteers who had taken quetiapine took placebo and vice versa.

The concentrations of Prl, Cor, ACTH and GH were measured in each blood sample.

Hormonal assay

Blood samples for Prl, Cor and GH assays were collected in tubes without additives; serum was separated by centrifugation and stored at -20°C . Samples for the ACTH assays were drawn into refrigerated tubes containing EDTA; serum was separated by refrigerated centrifugation and stored at -20°C .

Cor, GH and Prl levels were measured by an immunoenzymometric assay (Tosoh AIA System Analyses; Tosoh Corporation, Tokyo, Japan). The method sensitivities were 0.5 ng/ml for Prl, 0.1 ng/ml for GH, and 0.2 $\mu\text{g}/\text{dl}$ for Cor. The intra- and inter-assay coefficients of variation were 6.8% and 4.3% for Prl, 5.4% and 2.7% for GH and 5.9% and 6.7% for Cor respectively. ACTH levels were determined by a chemiluminescent enzyme immunoassay (Immulite System, DPC Diagnostic Products Corporation, Los Angeles, CA, USA). The sensitivity of the method was 10.0 pg/ml with intra- and inter-assay coefficients of variation of 6.1% and 8.3% respectively.

Side-effects

Side-effects were evaluated with a modified Ugvalg for Kliniske Undersgelser (UKU) side-effect rating scale (Lingjaerde et al., 1987), at 120 and 240 min after

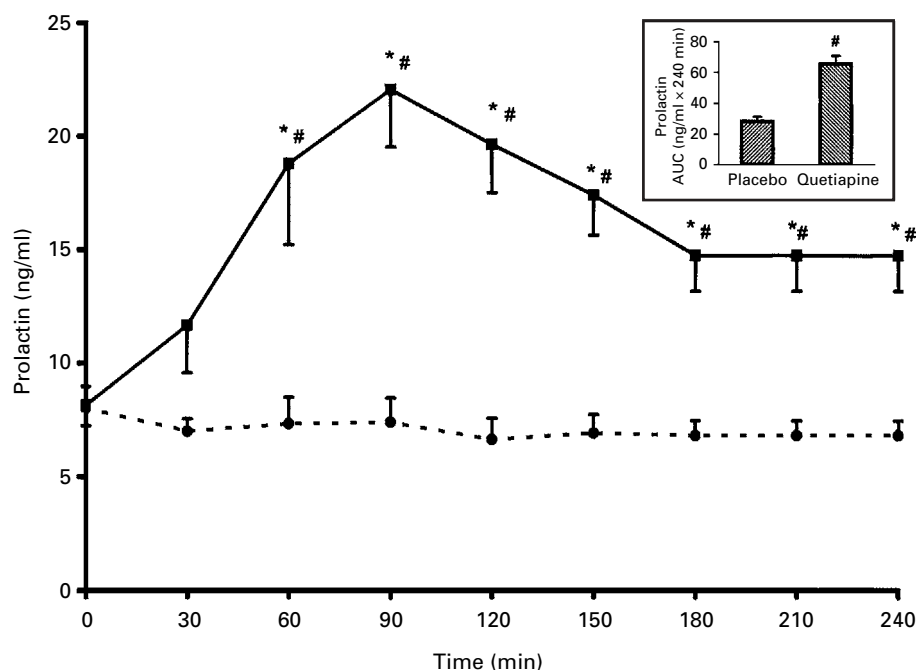


Figure 1. Mean (\pm s.e.) prolactin plasma levels (ng/ml) after the administration of 150 mg quetiapine (\blacksquare) and placebo ($-\bullet-$) to healthy volunteers ($n=15$). Two-way ANOVA factors: treatment $F(1, 14)=40.90$, $p<0.001$; time $F(8, 112)=4.84$, $p<0.001$; interaction $F(8, 112)=6.41$, $p<0.001$. Tukey's tests: * $p<0.05$, compared to baseline; # $p<0.01$, compared to placebo. Inset: mean (\pm s.e.) area under curve (AUC) for 150 mg quetiapine and placebo. Paired t test = 6.42, # $p<0.001$.

quetiapine or placebo administration. Among the four groups of side-effects assessed by the scale (psychic, neurological, autonomic and other), only items related to early side-effects, e.g. somnolence/sedation, dystonia, xerostomia and tachycardia, were evaluated.

Statistical analysis

Hormonal data were analysed with a two-way analysis of variance (ANOVA) for repeated measures (time: 0, 30, 60, 90, 120, 150, 180, 210, and 240 min; treatment: quetiapine, placebo) followed by Tukey's test when necessary. Greenhouse–Geisser and Huynh–Feldt corrections were used for the error term in the repeated-measures analysis.

Areas under the curve (AUCs), representing the Prl, Cor, ACTH and GH total secretions, were calculated with trapezoidal rule and compared using the Student's t test for paired samples.

In all tests, $p<0.05$ values were considered statistically significant.

Results

Prl baseline concentrations (mean \pm s.e.) were in the normal range for both quetiapine (8.13 ± 0.90) and

placebo (8.02 ± 0.95). In the placebo group, Prl serum concentration remained almost the same throughout the experiment. Thirty minutes after the administration of quetiapine, Prl concentration had increased. After 90 min, it had tripled the basal level (Figure 1).

Prl blood levels changed significantly after quetiapine [treatment factor, $F(1, 14)=40.90$, $p<0.001$], Prl levels changed significantly along the experiment in the quetiapine group [time factor, $F(8, 112)=4.84$, $p<0.001$] and there were significant differences in the treatment \times time interaction [interaction factor, $F(8, 112)=6.41$, $p<0.001$]. Prl levels did not change after placebo. After Greenhouse–Geisser and Huynh–Feldt corrections, differences remained significant.

Total Prl secretion during the experiment was significantly greater after the administration of quetiapine than after placebo. Indeed, the AUC for the Prl group was significantly greater than the one for the placebo group [quetiapine (mean \pm s.e.): 65.24 ± 20.91 ng/ml \times 240 min; placebo (mean \pm s.e.): 28.17 ± 11.71 ng/ml \times 240 min; $t=6.42$, $p<0.001$].

There was a decrease in Cor concentrations following both placebo and quetiapine during the 4 h of data collection (Figure 2). From 150 min onwards, such

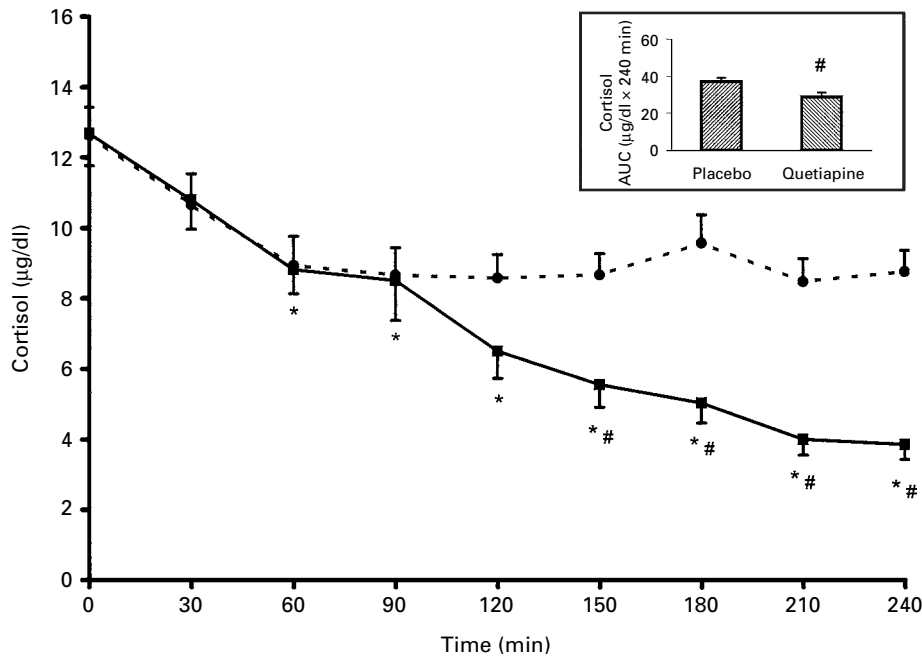


Figure 2. Mean (\pm S.E.) cortisol plasma levels ($\mu\text{g}/\text{ml}$) after the administration of 150 mg quetiapine (—■—) and placebo (---●---) to healthy volunteers ($n=15$). Two-way ANOVA factors: treatment $F(1, 14)=10.83$, $p<0.01$; time $F(8, 112)=26.82$, $p<0.001$; interaction $F(8, 112)=11.20$, $p<0.001$. Tukey's tests: * $p<0.001$, compared to baseline; # $p<0.001$, compared to placebo. Inset: mean (\pm S.E.) area under curve (AUC) for 150 mg quetiapine and placebo. Paired t test = 3.06, # $p<0.01$.

decrease was steeper in the quetiapine group than in the placebo one [treatment factor, $F(1, 14)=10.83$, $p<0.01$]. By the end of the experiment, Cor concentration with quetiapine was less than half of that with placebo. After quetiapine but not after placebo administration, there was a significant decrease in Cor levels [time factor, $F(8, 112)=26.82$, $p<0.001$]. There were significant interactions between time and treatment [interaction factor, $F(8, 112)=11.2$, $p<0.001$]. After Greenhouse–Geisser and Huynh–Feldt corrections, differences remained significant.

Total Cor secretion with quetiapine was lower than with placebo [quetiapine (mean \pm S.E.): $28.75 \pm 9.37 \mu\text{g}/\text{dl} \times 240 \text{ min}$; placebo (mean \pm S.E.): $37.12 \pm 8.21 \mu\text{g}/\text{dl} \times 240 \text{ min}$; $t=3.06$, $p<0.01$].

The minimum ACTH detectable value (10 pg/ml) was utilized instead of the results below the sensitivity limit, as this occurred with most samples (193 out of 270).

The decrease of ACTH concentrations was significant [time factor, $F(8, 112)=2.27$, $p<0.05$] and similar for both groups [treatment factor, $F(1, 14)=1.63$, $p>0.05$]. There was no significant treatment \times time interaction [interaction factor, $F(8, 112)=1.72$, $p>0.05$], neither did the total secretion of ACTH differ between the two groups [quetiapine

(mean \pm S.E.): $44.34 \pm 6.03 \text{ pg}/\text{ml} \times 240 \text{ min}$; placebo (mean \pm S.E.): $43.57 \pm 4.33 \text{ pg}/\text{ml} \times 240 \text{ min}$; $t=1.00$, $p>0.05$].

Several GH results were below the method sensitivity (125 out of 270), and thus, the minimum detection value used was 0.1 ng/ml.

As shown in Figure 3, GH concentrations were not significantly different with quetiapine and placebo up to 180 min. Then, there was an increase in the hormone levels for both groups [time factor, $F(8, 112)=7.17$, $p<0.001$], although this was more intense in the quetiapine group after 210 min. There were significant treatment \times time interactions [interaction factor, $F(8, 112)=3.88$, $p<0.001$]. There was no significant difference between quetiapine and placebo [treatment factor, $F(1, 14)=1.01$, $p>0.05$]. After Greenhouse–Geisser and Huynh–Feldt corrections, differences remained significant. The total GH secretion did not differ between the groups [quetiapine (mean \pm S.E.): $7.84 \pm 9.28 \text{ ng}/\text{ml} \times 240 \text{ min}$; placebo (mean \pm S.E.): $6.54 \pm 7.37 \text{ ng}/\text{ml} \times 240 \text{ min}$; $t=0.67$, $p>0.05$].

None of the volunteers reported side-effects with the use of placebo. After the ingestion of quetiapine, all of them had somnolence in the first evaluation ($t=120 \text{ min}$), as had 14 of them in the second evaluation ($t=240 \text{ min}$); approximately half of the

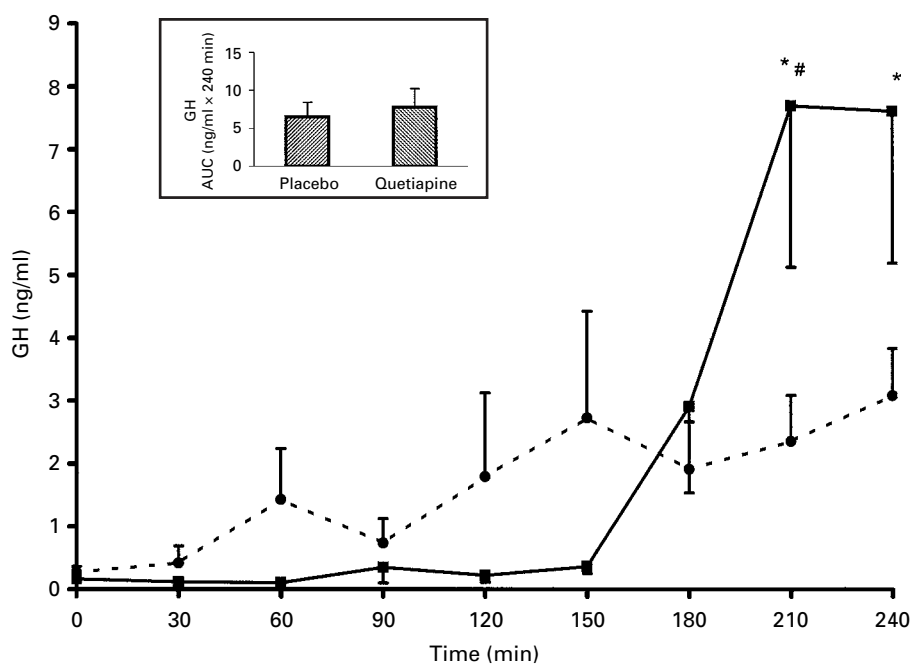


Figure 3. Mean (\pm S.E.) GH plasma levels (ng/ml) after the administration of 150 mg quetiapine (—■—) and placebo (---●---) to healthy volunteers ($n=15$). Two-way ANOVA factors: time $F(8, 112)=7.17$, $p<0.001$; interaction $F(8, 112)=3.88$, $p<0.001$; treatment $F(1, 14)=1.01$, $p>0.05$. Tukey's tests: * $p<0.001$, compared to baseline; # $p<0.05$, compared to placebo. Inset: mean (\pm S.E.) area under curve (AUC) for 150 mg quetiapine and placebo. Paired t test = 0.67, $p>0.05$.

volunteers (seven) had moderate somnolence in the middle of the experiment and mild somnolence at the end of observation period. Nine volunteers complained of mild xerostomia in the first evaluation, but only two of them in the second evaluation. In the first evaluation, four volunteers had dizziness, one tachycardia and another one headache, all of mild intensity.

Discussion

The increased Prl secretion found in this study is consistent with results from previous studies on the neuroendocrine effects of atypical antipsychotics (Gudelsky et al., 1987; Kapur and Remington, 2001; Kapur and Seeman, 2001; Turrone et al., 2002), including a recent one using quetiapine (Kapur et al., 2000). It is presumably secondary to the high transitory occupation of D_2 receptors at the anterior pituitary (Kapur et al., 2000; Turrone et al., 2002). However, our study design did not allow to an adequate evaluation of this transient Prl increase, since the last blood sample was only drawn up to 4 h after the administration of quetiapine.

The secretion of Prl, although mainly controlled by the dopaminergic system, is also under the influence

of other systems. Clinical studies have demonstrated histaminergic influences on the Prl secretion (Knigge et al., 1986a; Pontiroli et al., 1981). The hormonal stimulation mediated by H_1 receptors seemed related to inhibition of the dopaminergic system, whereas hormonal inhibition, via H_2 receptors, did not appear to involve dopamine (Knigge et al., 1986a). Interestingly, the role of histaminergic receptors on Prl secretion in rats depends on the route of histamine administration: the intracerebroventricular injection stimulates Prl, probably through H_2 receptors and promotes hormonal inhibition through H_1 receptors; whereas systemic administration induces opposite effects (Knigge et al., 1986b). Serotonergic stimuli increase Prl secretion in humans and in rats (Albinsson et al., 1994; Gartside and Cowen, 1990; Jørgensen et al., 1993, 1996; Lowy and Meltzer, 1988). This effect, in rats, seems to be a result of both the combined activation of 5-HT₁, 5-HT₂ and 5-HT₃ receptors and the interaction between 5-HT₁ and 5-HT₂ receptors with the H_1 and H_2 histaminergic receptors (Jørgensen et al., 1996). Sigma receptors might also participate in the control of Prl secretion via the modulation of the dopaminergic system (Eaton et al., 1996; Gudelsky and Nash, 1992), but results of studies in rats are controversial: ligands with a high affinity for these

receptors induce both increase (Gudelsky and Nash, 1992) and reduction of Prl concentrations (Eaton et al., 1996; Karbon et al., 1993). In addition, noradrenergic antagonism, via α_2 receptors, stimulates Prl secretion in rats, probably through a direct effect on the anterior pituitary (Kiem et al., 1995; Krulich et al., 1989).

It is conceivable that the quetiapine increase of Prl secretion was due to its dopaminergic effects as its antagonism of histaminergic and serotonergic receptors were not enough to counterbalance the dopaminergic stimulus. The plasma Prl levels were often higher than 20 ng/ml, although probably transitory, reaching a value considered as hyperprolactinaemia for men (Halbreich et al., 2003). There are several clinical effects of sustained hyperprolactinaemia and they have been well described, but it is still unknown whether daily Prl fluctuations, including values higher than those within the normal range, such as observed with some of the atypical antipsychotics, are completely safe. In fact, a recent study reported on delusions of pregnancy associated with increased Prl concentrations, probably due to the rising of the hormonal levels (Ali et al., 2003). Thus, it should be borne in mind that the statement 'atypical antipsychotics do not induce Prl elevation' may not be completely true as these brief and transient hormonal elevations need further studies, including long-term effects and potential clinical consequences.

The reduction of Cor concentrations after the administration of quetiapine may be due to its antagonism on H_1 , σ , α_1 , 5-HT₂ and D₂ receptors. It has been shown that these receptors' antagonism inhibit the release of Cor in humans (Asnis et al., 1992; Laakmann et al., 1999; Lowy and Meltzer, 1988; Monteleone et al., 1991; Sargent et al., 1998; Schilling et al., 1992; Schüle et al., 2002) and of corticosterone in rats (Bagdy, 1996; Eaton et al., 1996; Gudelsky and Nash, 1992; Owens et al., 1991; Tsujimoto et al., 1993). Quetiapine's antagonism on the α_2 adrenergic receptors was not enough to prevent the Cor decrease. Diurnal decline in Cor level at the time of the experiment may have contributed to these results but, as the reduction with quetiapine was steeper than that observed with placebo, pharmacological action was probably the main reason for the difference.

Studies have demonstrated that histaminergic activation in rats stimulates ACTH release (Knigge et al., 1989), probably through a release of oxytocin and corticotropin-releasing hormone (CRH) due to an increase of RNAm in hypothalamic neurons. This effect is mediated by both H_1 and H_2 receptors (Kjær et al., 1998). In humans, H_1 antagonists blunted the ACTH increase induced by hypoglycaemia or metyrapone

(Allolio et al., 1980). Besides, σ receptors agonists produced an increase in ACTH secretion in rats (Eaton et al., 1996; Iyengar et al., 1991; Pechnick and Poland, 1994), and such an effect did not seem to be caused by a direct action on the pituitary, since it did not happen *in vitro*, i.e. cultures of pituitary cells (Iyengar et al., 1990). Interestingly, the activation of α_1 adrenergic, 5-HT₂ serotonergic and D₂ dopaminergic receptors is capable of increasing ACTH secretion in rats (Borowsky and Kuhn, 1992; Calogero et al., 1993; Gartside and Cowen, 1990; Labrie et al., 1984; Levy and Van der Kar, 1992; Owens et al., 1991; Tuomisto and Mannisto, 1985). In humans, the activation of D₂ receptors in hypothalamic dopaminergic neurons also produced an ACTH increase (Tuomisto and Mannisto, 1985), but a study with four volunteers did not detect any change in this hormone secretion after the administration of ketanserin (a 5-HT₂ antagonist) (Gordin et al., 1985).

Thus, a reduction in ACTH levels was expected as a consequence of quetiapine's antagonistic action in H_1 , σ , α_1 , 5-HT₂ and D₂ receptors. However, there were no significant differences between the groups, probably due to the 'ground effect', i.e. most of the results were below the sensitivity of the assay. Unfortunately our study did not use any challenge test in order to stimulate ACTH release before the administration of quetiapine. Such limitation with the ACTH results may explain the contrast between Cor decrease and ACTH non-response. Since the secretion of both hormones is closely related (Aron et al., 2001), either the test was not capable of detecting a parallel ACTH decrease or a direct action in the adrenal glands was responsible for the Cor response.

The intracerebroventricular administration of histaminergic agonists in rats inhibits the pharmacologically induced GH release and its pulsatile secretion (Netti et al., 1982; Roberts and Calcutt, 1983). Therefore, quetiapine's high antagonism on H_1 receptors could stimulate GH secretion.

The antagonism of 5-HT₂ serotonergic receptors with ketanserin and ritanserin did not produce changes in GH basal levels in two studies with healthy volunteers (Gordin et al., 1985; Pontiroli et al., 1981). Another study in healthy volunteers, using the 5-HT₂ agonist MK-212, did not demonstrate significant changes in GH concentrations either (Lowy and Meltzer, 1988). The intravenous administration of 5-hydroxytryptophan (serotonin precursor) increases GH secretion but this effect may be mediated by dopaminergic rather than serotonergic neurotransmission (van Praag et al., 1986). The lack of response of GH levels to the blockade or the activation of

5-HT₂ receptors suggests that such an increase is mediated by other serotonergic receptors (Anderson and Cowen, 1986; Pontiroli et al., 1981). Agonists of the α_2 adrenergic receptors stimulate GH release (Amsterdam et al., 1989; Gaynor et al., 1993; Lima et al., 1993; Netti et al., 1993). A study with cattle (McMahon et al., 2001) suggests that the inhibition of somatostatin release, at the periventricular nucleus, and the direct stimulation of the GH releasing hormone (GHRH) release at the median eminence, would be the mechanisms responsible for the increase in GH. Dopaminergic (D₂) agonists, as well as α_2 adrenergic agonists, produce, in humans, increase of GH concentrations (de Visser et al., 2001; Schilling et al., 1992). The increase in GH levels in response to quetiapine could have been prevented by all these actions, but it did not occur. Besides pharmacological factors and in spite of the effort to keep volunteers awake to avoid sleep's interference on hormonal secretion, short naps could not be completely prevented and might have also contributed to GH increase. Pulsatile GH secretion (Finkelstein et al., 1972) could be another explanation to our results since medium GH increase was due to elevations from 8 out of 15 volunteers.

The somnolence induced by quetiapine has been attributed to the high affinity for H₁ receptors as well as the moderate affinity for α_1 receptors (Garver, 2000; Green, 1999). In this study, this effect was pronounced, possibly due to the administration of 150 mg quetiapine as an initial dose. This dose, although the low limit of the therapeutic range, is triple the recommended initial dose. It was chosen to evaluate quetiapine's effects within the therapeutic range instead of using subclinical doses. Dizziness could be another symptom of sedation, as well as somnolence (Garver, 2000; Green, 1999). Xerostomia cannot be explained by an action on muscarinic receptors, since quetiapine has a low affinity (IC₅₀ > 10 000 nM) for them. A reason for it may be the reduction of the cholinergic activity indirectly produced by the histaminergic (H₁) antagonism (Garver, 2000).

Further studies, measuring blood levels for quetiapine in a dose-response fashion, are necessary to confirm and clarify the present findings.

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Statement of Interest

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