Ziprasidone decreases cortisol excretion in healthy subjects

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Aims

To determine the influence of the atypical antipsychotic ziprasidone on cortisol excretion.

Methods

In a double-blind, placebo-controlled, randomized cross-over design 11 healthy male subjects were studied twice for 2 consecutive nights (N1, undisturbed sleep conditions; N2, exposure to acoustic stress) 5 days apart. Placebo or ziprasidone 40 mg was administered orally 2 h before bedtime on N1 and N2. Urine was collected during three fractionated collection periods (evening; night; morning) for the later determination of cortisol concentrations by standard radioimmunoassays.

Results

Ziprasidone decreased the total amount of cortisol excreted by 4.9 (95% CI 3.3, 6.5) μg during N1 and by 10.8 (95% CI 5.7, 15.8) μg during N2 ($P < 0.002$). This effect was still detectable in the morning ($P < 0.02$), with decreases of 5.8 (95% CI -2.8 , 14.4) μg after N1 and by 12.1 (95% CI 2.8, 21.4) μg after N2. The effect subsided in the evening. A significant intervention-condition interaction ($P < 0.02$), was found. The significant increase in cortisol excretion during acoustic stress observed with placebo was absent after treatment with ziprasidone.

Conclusions

The significant decrease in nocturnal cortisol excretion following ziprasidone reflects a decreased activity of the HPA-axis in healthy subjects. This effect may be an important contributor to the mode of action of ziprasidone in different patient populations, particularly in the treatment of depression and in cognitive impairment in schizophrenia.

Introduction

Atypical antipsychotics have recently been shown to have beneficial effects in the treatment of affective disorders. In addition to their use in schizophrenia, quetiapine, olanzapine and ziprasidone have antidepressive effects either as add-on treatment or as monotherapy [1–3], that might be related to their influence on the hypothalamopituitary adrenal (HPA) axis.

Abnormalities in the regulation of the HPA axis have been demonstrated for different psychiatric disorders with most consistent findings being for major depression. Among other parameters reflecting an increased activity of the HPA axis, elevated cortisol concentrations were found in depressed as well as schizophrenic patients [4]. Hypercortisolaemia in depression has been linked to several health problems such as hypertension,

increased abdominal fat, decreased bone density, and cognitive impairment [5]. Decreasing cortisol concentrations by the administration of glucocorticoid synthesis inhibitors improves the HPA-axis abnormalities and is associated with a decrease in depressive symptomatology [6].

Elevated cortisol concentrations and dexamethasone nonsuppression have also been consistently found in patients suffering from schizophrenia [7–9]. Furthermore, plasma concentrations of ACTH and cortisol correlate positively with negative symptomatology in schizophrenic patients [10, 11] and negatively with cognitive performance in a larger group of patients and controls [12]. Additionally, persistent hypercortisolaemia in schizophrenia is associated with poor outcome and ventricular enlargement [13].

Despite their usefulness in the treatment of depression and schizophrenia, only limited information exists on the effects of atypical antipsychotics on cortisol secretion and HPA-activity. The atypical antipsychotics clozapine, olanzapine, and quetiapine, but not amisulpiride, have been shown to reduce circulating cortisol concentrations in both schizophrenic patients and healthy subjects [14–19].

There are no published data on the effects of ziprasidone on HPA-axis activity. Ziprasidone affects different neurotransmitter systems involved in the regulation of the HPA axis. The drug is a serotonin-2A (5-HT_{2A})/dopamine D₂ antagonist and exhibits potent interaction with 5-HT_{2C}, 5-HT_{1D}, and 5-HT_{1A} receptors in human brain tissue [20, 21]. Ziprasidone is an antagonist at the 5-HT_{2C} receptor and an agonist at the 5-HT_{1A} receptor [20]. Furthermore, inhibition of serotonin and norepinephrine reuptake has been described [22].

Acute administration of medication which potentiates serotonin or noradrenaline function stimulates the activity of the HPA axis [23]. On the other hand, blockade of 5-HT_{2A/C} receptors antagonizes cortisol elevation in challenge experiments [24, 25], whereas 5-HT_{1A} agonism is associated with an increase in ACTH and cortisol concentrations [26]. However, it is not known whether ziprasidone exerts greater inhibitory or excitatory influences on HPA-axis activity.

The present study examined the influence of ziprasidone on nocturnal urinary excretion of cortisol in healthy subjects. Collecting nocturnal urine minimizes the potential effects of physical and mental stressors occurring during the daytime and provides a more reliable estimate of treatment differences in basal nocturnal cortisol excretion. In addition to evaluation during undisturbed sleep (night 1) subjects were studied on

night 2 following exposure to an acoustic stimulus, used as a standardized psychological stressor [18].

Methods

Subjects

A total of 16 healthy male subjects (mean age 26 ± 4.4 years, range 20–35 years) were included in the study after a clinical history, a physical examination, an electrocardiogram, and routine laboratory examinations. Subjects were excluded if they suffered from sleep disorders, affective disorder, schizophrenia, delusions, epilepsy, obsessive-compulsive disorder, social phobia, alcohol or drug dependence, sensitivity to ziprasidone, cardiovascular disease (myocardial infarction, heart insufficiency, ECG-conduction abnormalities), serious medical problems requiring treatment, cerebrovascular disease, liver disease, and any condition predisposing to arterial hypotension, e.g. dehydration, hypovolaemia, or if they were taking psychotropic or antihypertensive medication. None of the subjects had undertaken long distance travel during the 4 weeks before the study.

Study design

This work was part of a larger study investigating the influence of ziprasidone on sleep and urinary cortisol excretion using a randomized, double-blind, cross-over, placebo-controlled, single-centre design. We presumed that nocturnal collection of urine would minimize the potential effects of physical and mental activity during daytime and provide a more reliable estimate of treatment differences in basal cortisol excretion. Polysomnographic results will be reported elsewhere. Screening of subjects usually preceded randomization by a maximum of 14 days. Each subject was studied for a total of 5 nights. One polysomnographic screening night preceded the experimental sessions in order to exclude sleep disorders. After inclusion, subjects were tested during two sessions, each of 2 consecutive nights, separated by a 5 day wash-out period. On night 1 (N1) hormone excretion during undisturbed sleep was monitored, whereas on night 2 (N2) subjects were exposed to an acoustic stimulus to evaluate the effects of external stress. The same medication was given during N1 and N2 of each session in a randomized order between session 1 and 2. Medication was administered orally 2 h before bedtime with a small snack. Urine was collected over the following periods: (evening: 19.00 h–23.00 h; night: 23.00 h–07.00 h; morning: 07.00 h–11.00 h). The study followed the declaration of Helsinki and was approved by the local ethics committee of the Department of Medicine. Subjects gave written informed consent and were paid an honorarium of Euro 300.

Acoustic stress

Subjects were exposed to acoustic stress during N2 as described earlier [27]. For generation of tones the composition music software CUBASIS VST 3.0 was used. An identical tone program was used on each occasion. Acoustic stress was started at bedtime and ended on final awakening.

Urine collection and hormonal analysis

For stabilization of urine contents, 0.5 g EDTA (ethylenediamine tetraacetic acid) and 0.5 g of sodium metabisulfite were added to the urine containers provided to each subject. Before the start of the collection period subjects emptied their bladder. The volume of the urine voided during the three designated periods was determined and aliquots of 10 ml were frozen at -35°C . Urinary cortisol concentration was measured by direct radioimmunoassay, as described elsewhere [28]. Inter-assay variance was 10% with a detection limit of $3.75\text{ pg } 100\text{ }\mu\text{l}^{-1}$. Cortisol excretion was calculated as the product of urine volume and hormone concentration for each collection period.

Statistical analysis

The distribution of the cortisol concentration data was tested using the Kolmogorov-Smirnov-test. Results were expressed as means and 95% confidence intervals. Analyses of variance (ANOVA) with repeated measures were used to evaluate the main effects of treatment (placebo, ziprasidone 40 mg) and intervention condition (undisturbed or acoustic stress) for cortisol excretion during each collection period. If the F values were significant, *post hoc* tests were performed in order to compare the periods of undisturbed sleep with those of acoustic stress in the placebo group and to compare the effects of 40 mg ziprasidone with placebo for both conditions separately. The level of significance was set at $P < 0.05$. The statistical package STATISTICA 6.1[®] was used for the analysis.

Results

Owing to technical problems on one night in two subjects, withdrawal of consent for the acoustic stress phase (N2) of one subject, side-effects (brief fainting but with total recovery) during treatment with ziprasidone in a further subject, and inability of one subject to urinate at the required time (during placebo), data were analyzed from 11 subjects.

The data were normally distributed. Table 1 shows the concentrations and total amounts of cortisol excreted in the urine for all conditions and collection periods, as well as F and P values based on ANOVAs. Evening cor-

tisol excretion was not significantly different between the treatment and intervention conditions. Thus, carry over effects were not observed in the evening hours before N2.

For the 23.00 h–07.00 h collection period significant effects of condition (undisturbed vs. acoustic stress condition) and treatment (placebo vs. ziprasidone 40 mg) as well as a significant interaction of condition $\times$ treatment on the total amount of cortisol excreted were found. During N1 cortisol excretion was significantly lower after ziprasidone, which decreased total amount recovered in urine compared with placebo by 4.9 (95% CI $3.3, 6.5$) μg during N1, but not in the evening. During N2 acoustic stress significantly elevated cortisol excretion. In comparison with placebo ziprasidone decreased the total amount of cortisol excreted by 10.8 (95% CI $5.7, 15.8$) μg during N2. Further analysis of the interaction of intervention $\times$ condition demonstrated that the significant increase in cortisol excretion during acoustic stress observed with placebo treatment did not occur with ziprasidone treatment. Similar results were found for urine cortisol concentration.

During the morning collection period (07.00 h–11.00 h), a significant decrease in the total amount of cortisol excreted was found after ziprasidone administration compared with placebo (by 5.8 (95% CI $-2.8, 14.4$) μg after N1 and by 12.1 (95% CI $2.8, 21.4$) μg after N2). No significant effects of intervention (undisturbed or acoustic stress) or interaction of intervention $\times$ treatment were found.

Discussion

The atypical antipsychotic ziprasidone significantly decreased urinary cortisol excretion and antagonized the stress mediated increase in cortisol recovery during acoustic stimuli. The cortisol lowering influence of ziprasidone was still observable some 14 h after administration of the drug, whereas by 24 h the effect had abated.

These results are comparable with the effects of the atypical antipsychotic quetiapine studied under similar conditions [18], but are in contrast with the finding of unchanged cortisol secretion seen after acute administration of amisulpride in healthy subjects [19].

The influence of two other atypical antipsychotics clozapine and olanzapine on HPA function has been studied in schizophrenic patients. However, the observed decrease in ACTH and/or cortisol concentrations and attenuated responses to the serotonin receptor agonist *m*-chlorophenylpiperazine after treatment with clozapine [29, 30] may have been confounded by the parallel effect of psychopathology related stress. The

Table 1

Urinary cortisol excretion in 11 healthy subjects after the administration of placebo, and ziprasidone 40 mg at 21.00 h studied during 2 nights under undisturbed sleep (N1) and acoustic stress that was applied during the bedtime period between 23.00 h and 07.00 h (N2). Data are presented as means and 95% confidence intervals, *P* values in bold

Intervention Treatment	N1 (standard sleep laboratory conditions) Placebo	40 mg ziprasidone	N2 (acoustic stress) Placebo	40 mg ziprasidone	Intervention effect (N1 vs. N2) ANOVA <i>F</i> (1, 11) <i>P</i> <	Treatment effect (placebo vs. 40 mg ziprasidone) ANOVA <i>F</i> (1, 11) <i>P</i> <	Interaction of treatment and intervention <i>F</i> (1, 11) <i>P</i> <
Means of total amount of cortisol excretion in mg (95% confidence interval)							
19.00 h–23.00 h	6.0 (3.7, 8.2)	7.8 (5.7, 9.8)	7.1 (5.4, 8.8)	6.8 (4.8, 8.8)	0.02, 0.90	0.48, 0.50	1.321, 0.28
23.00 h–07.00 h	14.3 (10, 18.7)	9.5 (5.5, 13.4)	22.6 (16, 29.1)	11.8 (8.1, 15.5)	8.27 0.02	36.31 0.0002	7.69 0.02
07.00 h–11.00 h	23.8 (13.5, 34.1)	17.9 (11.4, 24.5)	29.9 (20.7, 39.1)	17.8 (14.2, 21.4)	0.58 0.47	8.63 0.02	1.45 0.26
Means of urinary cortisol concentration in ng ml ⁻¹ (95% confidence interval)							
19.00 h–23.00 h	20.7 (15, 26.4)	20.7 (15.9, 25.6)	18.4 (12.9, 23.9)	18.9 (12.5, 25.2)	2.27 0.16	0.03 0.88	0.03 0.86
23.00 h–07.00 h	28.2 (19.6, 36.8)	15.4 (11.2, 19.6)	40.0 (31.5, 48.6)	18.9 (12.8, 24.9)	18.02 0.002	2.27 0.16	0.03 0.88
7.00 h–11.00 h	71.8 (56.3, 87.3)	92.2 (62.6, 121.8)	75.1 (55.2, 95)	72.0 (48.3, 95.6)	1.85 0.20	28.36 0.0005	4.1 0.7
						0.46 0.51	3.46 0.09

latter was also related to elevated glucose concentrations in these patients [31], which could be a consequence of the diabetogenic effect of cortisol. However, some atypical antipsychotics, including clozapine and olanzapine, have been demonstrated to cause adverse effects on glucose regulation [32] and therefore, other mechanisms have to be involved. The typical antipsychotic fluphenazine had no effect on cortisol concentrations [29] in schizophrenic patients. The majority of studies investigating the influence of typical antipsychotics on cortisol in healthy subjects reported mostly unchanged concentrations after acute or subchronic administration. One group found increased cortisol concentrations after haloperidol administration, whereas in an other study haloperidol antagonized heat stress-induced increases in cortisol [for a review see reference 18].

Several mechanisms might be involved in the ziprasidone-mediated decrease in circulating cortisol concentrations and, therefore, in cortisol excretion. The agonist action of ziprasidone at the 5-HT_{1A} receptor [20] and its inhibition of norepinephrine and serotonin reuptake [22] must be assumed to increase rather than to decrease HPA activity [23, 26]. However, a complex interaction of the effects usually observed after reuptake inhibition and further direct effects of ziprasidone on serotonergic receptors may be important. The decreased cortisol concentrations observed after administration of olanzapine and clozapine to schizophrenic patients have been attributed to 5-HT₂ receptor blockade [14–17, 33].

5-HT_{2A/C} receptors play an important role in the regulation of the HPA axis. Usually, ACTH and/or cortisol concentrations increase after the administration of meta-chlorophenylpiperazine (MCP), 5-hydroxytryptophane, or fenfluramine. Premedication with the 5-HT_{2A/C} antagonist ritanserin attenuates the MCP- and 5-HT-induced increases in cortisol [24, 34] although some studies have reported suppressed elevation of cortisol concentrations by ritanserin through a mechanism involving 5-hydroxytryptophan [35]. Furthermore, ritanserin given as a single dose decreases ACTH and cortisol concentrations [36], and the marked increase in corticosteroid concentrations produced by fenfluramine and quipazine are abolished by pretreatment with ketanserin [37]. Recently, further consideration of the effects of 5-HT agonists indicated that 5-HT_{2A} receptors rather than 5-HT_{2C} receptors play an important role in mediating increases in rat serum corticosterone concentrations [25, 38].

Based on the above considerations, it appears likely that blockade of 5-HT₂ receptors by ziprasidone may be primarily responsible for the decrease of cortisol excretion. In this context, we also found that quetiapine, an

atypical antipsychotic with predominant 5-HT_{2A} antagonism relative to its low affinity for the 5-HT_{2C} receptor, also decreases cortisol excretion [18]. Furthermore, the lack of influence on cortisol concentrations observed after the administration of amisulpride [19] is compatible with this mechanism of action of ziprasidone since amisulpride is a selective dopamine D₂/D₃ receptor blocker without significant activity at 5-HT₂ receptors. However, the weak or absent influence of ritanserin and ketanserin on baseline cortisol concentrations [39] indicates that other mechanisms may also be involved in the interaction of ziprasidone with cortisol.

Although ziprasidone demonstrates only weak antagonism at histamine H₁ and α_1 -adrenergic receptors, an effect on of these and perhaps other receptors should also be considered as a basis for the decrease in cortisol excretion. Blockade of these receptors has been demonstrated to decrease cortisol concentrations or to antagonize their elevation in challenge experiments [40].

The present study investigated the effect of ziprasidone on cortisol excretion in healthy subjects. Cortisol is an important factor in the pathophysiology of major depression and schizophrenia. The clinical significance of the cortisol lowering effect of ziprasidone should be explored in further studies of these patient groups. Areas of investigation should also include the secondary long-term effects of elevated circulating cortisol, e.g. hypertension, increased abdominal fat, decreased bone density, and cognitive impairment [5], negative symptomatology [10, 11], and brain morphology [13].

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