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The effects of olanzapine and fluphenazine on plasma cortisol, prolactin and muscle rigidity in schizophrenic patients: a double blind study

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Short title: Olanzapine vs. fluphenazine in schizophrenia

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2.1. Abstract

Pharmacotherapy of schizophrenia is associated with the stressful side effects. Muscle rigidity causes distress, discomfort and poor compliance. The aim of the study was to determine the relationship between plasma hormones (cortisol and prolactin /PRL/) and muscle rigidity in female schizophrenic patients treated with olanzapine or fluphenazine. In a randomized, double-blind 22-weeks study, 12 patients were treated with olanzapine (5-20 mg/day) and 10 patients received fluphenazine (6-21 mg/day). Treatment with olanzapine moderately decreased, while treatment with fluphenazine significantly increased plasma cortisol levels and muscle rigidity. The marked and moderate increase in plasma PRL levels were found in patients treated with fluphenazine and olanzapine, respectively. The results suggested that olanzapine induced moderate neuroendocrine effects and a reduction in rigidity as compared to fluphenazine treatment.

2.2. Key words: cortisol, fluphenazine, olanzapine, prolactin, rigidity, schizophrenia

2.3. Abbreviations: one-way analysis of variance (ANOVA), extrapyramidal side effects (EPS), Positive and Negative Syndrome Scale (PANSS), prolactin (PRL)

3.1. Introduction

The pharmacotherapy of schizophrenia (Kane, 2001) is often associated with the extrapyramidal side effects (EPS) related to the blockade of dopamine D₂ receptors in the basal ganglia (Crocker and Hemsley, 2001) and disturbance of dopaminergic and serotonergic/cholinergic systems. Muscle rigidity and other EPS cause distress, discomfort and poor compliance. Stress hormones prolactin (PRL) and cortisol are related to distress response (Jakovljevic et al., 1991; Tandon and Halbreich, 2003). Olanzapine is an atypical antipsychotic of the thienobenzodiazepine class. New antipsychotics induce a moderate blockade of D₂ receptors and generate a more subtle functional motor impairment and better treatment response (Putzhammer et al., 2005) than conventional antipsychotics, like fluphenazine. Fluphenazine reduces psychotic symptoms, but induces different side effects (Mortimer, 1994) due to its action achieved via D₁ and D₂ receptors (Coirini et al., 1997; Meltzer and Nesh, 1991).

Since olanzapine and fluphenazine differ in their side effects profile and clinical efficacy (Dossenbach et al., 2004), our hypothesis was that olanzapine and fluphenazine would differently affect plasma cortisol, PRL and muscle rigidity. The aim of the present study was to determine, in the smaller group of female schizophrenic patients extracted from the previous multicentric double blind study (Dossenbach et al., 2004), the effects of olanzapine or fluphenazine on plasma PRL and cortisol levels, and muscle rigidity after long term (22-weeks) treatment.

3.2. Subjects and methods

In a randomized, double blind 22-week study, 22 female schizophrenic (DSM-IV criteria; American Psychiatric Association, 1994) patients (mean age \pm SD, 33.2 \pm 8.8 years) were treated with either olanzapine (N=12) or fluphenazine (N=10) in the Clinical Hospital Centre Zagreb.

Patients were part of the group included in a multicentric clinical trial (Dossenbach et al., 2004). The Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) was used to evaluate schizophrenic symptoms, and baseline total PANSS scores were 96.9 ± 15.4 for fluphenazine, and 107.7 ± 19.1 for olanzapine-treated patients, respectively.

On admission, 12 patients (5 assigned to olanzapine and 7 to fluphenazine) had been drug free for about 1 year. None of the patients received depot neuroleptics. Other patients were medicated with haloperidol and clozapine, with a similar distribution of previous haloperidol (15 mg/day) users among two treatment groups. Samples were taken after a wash-out of at least 7 days before and after 22-weeks of treatment with olanzapine (dose 5-20 mg; mean 12.8 ± 2.8 mg/day) or fluphenazine (6-21 mg; mean 10.5 ± 2.5 mg/day). Concomitant psychoactive medications were not allowed, except benzodiazepines for sleep disturbances and/or severe anxiety. Each group consisted of one menopausal patient. In the pre-menopausal patients blood samples were collected between 1st and 7th day of the menstrual cycle. All participants provided written informed consent prior to the study entry.

Cortisol (nmol/L) and PRL (ng/ml) were measured in plasma by a radioimmunoassay and immunoradiometric assay (Diagnostic Products Corporation, USA) with detection limit of 5.5 nmol/L and 0.1 ng/ml, and intra- and inter-assay coefficients of variation 4.7% and 5.2% for cortisol and 1.6% and 2.8% for PRL, respectively. Clinical ratings and biochemical measures were made blind to each other.

Rigidity assessment was performed using computerized instrumental measurement by elbow device "Tonometre" (Relja et al., 1996). A patient was comfortable seated in a chair, with the tested forearm supported horizontally on an arm board of the tonometre. The rigidity registration was carried out through 20 consecutive cycles (flexion and extension). The first 10

measurements were preparatory, aimed to achieve maximal relaxation of the patients. The second 10 cycles were transmitted and evaluated, with the results expressed in Newton meters (Nm), as mean \pm SD of 10 measurements (Relja et al., 1996).

Statistical evaluation of the results, expressed as mean \pm SD, was done using one-way analysis of variance (ANOVA), two-way ANOVA, repeated measures analysis of variance (RMANOVA) and Newman Keuls' test, Pearson's coefficient of correlation, and Student t-test (for comparisons between two groups). The significance level was $p < 0.05$. The statistical package used was SigmaStat 2.0.

3. 3. Results

Before treatment plasma cortisol levels did not differ significantly ($p > 0.05$) among schizophrenic patients (Fig 1A). After 22-weeks of treatment (Fig. 1A), plasma cortisol levels differed significantly ($F=8.85$; $df=4,61$; $p < 0.001$), with a significant ($p < 0.05$) fluphenazine-induced increase (24.5%), as compared to olanzapine-induced decrease (15%) of cortisol levels. A significant effect of olanzapine or fluphenazine treatment ($F=5.47$; $df = 1,43$; $p < 0.025$), and a significant interaction between treatment and time (22-weeks vs. baseline) ($F=4.56$; $df = 1,43$; $p < 0.039$) on plasma cortisol levels was found (two-way ANOVA).

Treatment with either olanzapine or fluphenazine significantly ($F=16.5$; $df=3,45$; $p < 0.001$) increased plasma PRL levels (Fig. 2), with a significant ($p < 0.05$) fluphenazine (87%) or olanzapine (35%) induced increase of plasma PRL levels when compared to baseline values. Plasma PRL levels were significantly higher ($p < 0.05$) after fluphenazine than after olanzapine treatment (Fig. 2). A significant ($F=12.94$; $df = 1,43$; $p < 0.0001$) effect of treatment (olanzapine vs.

fluphenazine), and time ($F=12.05$; $df=1,43$; $p<0.001$) (22-weeks vs. baseline), on plasma PRL levels was found (two-way ANOVA).

Baseline mean rigidity values in schizophrenic patients (1.71 ± 0.84 Nm) were slightly higher than those in healthy control (1.58 ± 0.96 Nm), (Relja et al. 1996). Treatment with olanzapine significantly ($F= 7.53$, $df= 1,11$; $p = 0.019$) decreased, while treatment with fluphenazine significantly ($F= 7.08$, $df= 1,9$; $p= 0.026$) increased the rigidity values (Fig. 1B), respectively (RMANOVA).

Although olanzapine or fluphenazine treatment affected significantly and in an opposite manner the rigidity and plasma cortisol values in schizophrenic patients, there was no significant ($p>0.05$) correlation between muscle rigidity and plasma cortisol before ($r = 0.25$ and $r= -0.16$) or after ($r= 0.35$ and $r= -0.27$) treatment with fluphenazine or olanzapine, respectively.

Age of the patients did not differ significantly ($t=1.68$; $df=20$; $p=0.11$, Student's t-test) between those treated with olanzapine (29.5 ± 8.4 , range 20-46 years) or fluphenazine (35.6 ± 8.3 , range 20-52 years). No significant correlation between age and plasma cortisol ($r = -0.15$; $p=0.50$), or age and plasma PRL ($r=-0.30$; $p=0.17$) levels was found.

3. 4. Discussion

The results of the present study showed the opposite effects of treatment with olanzapine and fluphenazine on plasma cortisol values and muscle rigidity, indicating that schizophrenic patients receiving olanzapine might have been exposed to a smaller amount of EPS-related distress than those treated with fluphenazine. The improvement in the muscle rigidity confirms the favorable profile of olanzapine in the treatment of schizophrenia (Tandon and Halbreich, 2003; Dossenbach et al., 2004). The opposite neuroendocrine effects of olanzapine and fluphenazine on plasma

cortisol levels in schizophrenic patients (present study), and the “normalization” of the HPA axis hyperactivity (Muck-Seler et al., 1999; Ryan et al., 2004), support the assumption that the suppression of the HPA axis hyperactivity is related to the treatment response (Tandon and Halbreich, 2003).

The HPA axis activity might be influenced by different factors such as gender, stress, psychiatric comorbidity, previous medication, older age, or different phases of menstrual cycle. To exclude these factors, only female patients, part of the bigger, large multicentric study (Dossenbach et al., 2004) were included, matched for previous medication and the level of stress. Patients with comorbid diagnoses and those who received depot neuroleptics were excluded. No correlation between age and plasma cortisol levels was found in the present and previous studies (Muck-Seler et al., 1999; Seeman and Robbins, 1994). To avoid the possible influence of menstrual phases on the HPA activity (Leibenluft et al., 1994), patients were sampled in the follicular phase, and previously we have shown that pre- or post-menopausal status did not affect significantly plasma cortisol levels in schizophrenic patients (Muck-Seler et al., 2004).

Hyperprolactinemia is a common side effect of typical antipsychotics (Halbreich et al., 2003; Petty, 1999), while atypical antipsychotics especially olanzapine, are PRL-sparing drugs (Dickson and Glazer, 1999). In our study fluphenazine induced more pronounced PRL increase than olanzapine. If a magnitude of the hyperprolactinemia may be used as a biological marker for the therapeutic effects of antipsychotic drugs (Halbreich et al., 2003), higher PRL levels found after fluphenazine than after olanzapine treatment are in line with the better treatment response in olanzapine than in fluphenazine treated schizophrenic patients (Dossenbach et al., 2004).

The limitation of the study is a lack of multiple sampling of plasma cortisol and PRL levels, while its advantage lays in a randomized, comparative and double blind 22-weeks design. However, our results on the slight decrease in cortisol and moderate increase in PRL levels after olanzapine treatment agree with the nocturnal hormone profile in schizophrenic patients treated with olanzapine (Mann et al., 2006). On the other hand, olanzapine treatment did not affect significantly plasma cortisol or PRL levels in healthy controls sampled at a similar time-point (i.e. at 9.00 a.m., Cohrs et al., 2006). This difference in the results between healthy and schizophrenic subjects is presumably due to the abnormal HPA axis in schizophrenia (Tandon et al., 1991; Muck-Seler et al., 1999; Mann et al., 2006).

The different neuroendocrine effects of the two antipsychotics are due to their different pharmacological profile. Olanzapine is a potent antagonist of 5-HT_{2A} and D₂ receptors, with higher affinity for 5-HT_{2A} than for D₂ receptors (Bymaster et al., 1996; Richelson and Souder, 2000; Nyberg et al., 1997). Its beneficial effect is related to its combined 5-HT_{2A}/5-HT_{2C} and D₂ blocking properties, which results in the suppression of PRL secretion (Markianos et al., 2001), while fluphenazine blocks D₂ receptors which increase PRL release (Coirini et al., 1997).

In conclusion, our results showed that atypical antipsychotic olanzapine had a favorable effect on the muscle rigidity and better neuroendocrine profile than conventional neuroleptic fluphenazine.

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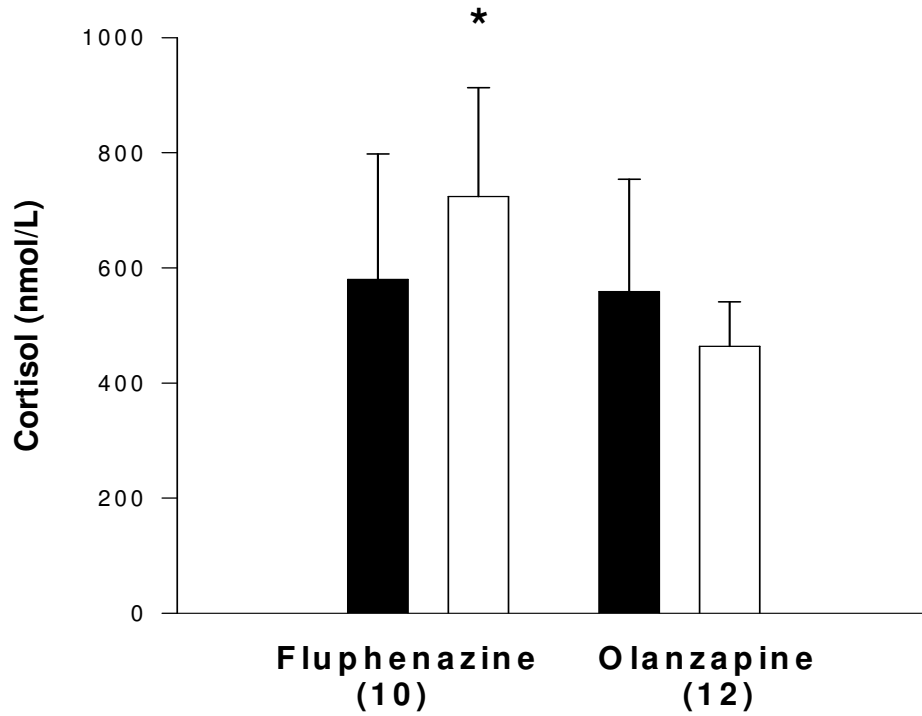
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Legends for figures

Fig 1. Plasma cortisol levels (nmol/L) (A) and muscle rigidity (Nm) (B) in schizophrenic patients before and after treatment with olanzapine or fluphenazine. Each column represents mean \pm SD. Number of subjects is given in brackets. * $p < 0.05$ vs. olanzapine after treatment, ** $p < 0.05$ vs. olanzapine before treatment (ANOVA followed by Newman-Keuls' test).

Fig 2. PRL (ng/ml) levels in schizophrenic patients before and after treatment with olanzapine or fluphenazine. Each column represents mean \pm SD. Number of subjects is given in brackets. * $p < 0.05$ vs. fluphenazine before treatment; ** $p < 0.05$ vs. olanzapine after treatment (ANOVA followed by Newman-Keuls' test).

A



B

