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Letter to the Editors

The lack of effect of ziprasidone on platelet serotonin concentration in schizophrenic patients

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Abstract

Rationale Ziprasidone is an atypical antipsychotic, with the unique multireceptor-binding profile. If affects multiple serotonergic (5-HT) receptors, inhibits 5-HT transporter (5-HTT) and inhibits synaptic 5-HT reuptake. These effects might be responsible for the antidepressant effect of ziprasidone.

Objectives Since there is a lack of *in vivo* data on the effects of ziprasidone on 5-HT concentration in humans, the aim of the study was to investigate the effect of ziprasidone

treatment on platelet 5-HT concentration in patients with schizophrenia or schizoaffective disorders.

Methods In and open-label study, the effect of ziprasidone (average dose of 109 mg/day) on platelet 5-HT concentration (determined fluorimetrically) was evaluated at baseline and after 7 and 28 days of treatment in 21 male and female patients with schizophrenia or schizoaffective disorders.

Results Ziprasidone treatment for 7 or 28 days did not significantly change baseline platelet 5-HT concentration in male and female schizophrenic patients. Platelet 5-HT concentration was not correlated with gender, age and smoking status of patients.

Conclusions There was a lack of effect of ziprasidone treatment on platelet 5-HT concentration in male and female schizophrenic patients. Although the clinical effects of ziprasidone were evident after 28 days of treatment, and ziprasidone has the highest potency among atypical antipsychotics to block 5-HTT, our data did not confirm the hypothesis that ziprasidone treatment decreases platelet 5-HT concentration, at least not in the doses used in our study.

Key words Ziprasidone · Platelet serotonin · Schizophrenia · Male and female patients

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and were therefore in line with the guidelines of the Declaration of Helsinki. There is no conflict of interest in relation to this article.

Ziprasidone is an atypical antipsychotic, with higher ratio of 5-HT2A/D2, 5-HT2C/D2 and 5-HT1A/D2 receptor binding than other antipsychotic drugs (Schmidt et al. 2001; Stahl and Shayegan 2007). It also blocks the serotonin transporter (5-HTT) and inhibits synaptic 5-HT reuptake (Tatsumi et al. 1999). Drugs that block the 5-HTT such as selective serotonin reuptake inhibitors (SSRI) have antidepressant properties, and ziprasidone is reported to have antidepressant effects in patients with depression (Moeller et al. 2007; Stahl and Shayegan 2007). At present, however, it is unknown whether ziprasidone affects the 5-HTT *in vivo* when given to patients in therapeutic doses. Platelet 5-HT concentration is a reliable marker of the 5HTT blockade induced by SSRI, and reduced platelet 5-HT concentration is used as a marker of the biological activity of various SSRI (Muck-Seler et al. 2002). Therefore, the aim of the study was to investigate the effect of ziprasidone treatment on platelet 5-HT concentration in patients with schizophrenia or schizoaffective disorders. The hypothesis was that, if ziprasidone blocks 5-HTT, it will reduce platelet 5-HT concentration.

An open-label, flexible-dose study included 21 (8 female and 13 male) patients with schizophrenia or schizoaffective disorder treated with ziprasidone (109.0 ± 27.1 mg/day, range 80-160), diagnosed using Structured Clinical Interview based on DSM-IV criteria, who were hospitalized due to inefficacy or adverse events of previous antipsychotic medication, or who stopped taking their antipsychotics prior to hospitalization. Exclusion criteria: treatment with ziprasidone, SSRI, tricyclic antidepressants or any other drug known to affect serotonin uptake in previous 4 weeks, past adverse reactions to ziprasidone, dementia, any other organic mental disorder, severe psychosis, severe depression, substance abuse and dependence in previous 3 months, abnormal ECG, the corrected (QTc) interval exceeding 450 ms. Benzodiazepines and hypnotics were allowed throughout the study. Anticholinergics were not routinely prescribed, but were allowed in the case of the emergence of extrapyramidal symptoms. Study was approved by the Ethics Committee of the University Hospital Centre

Zagreb, and has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. All subjects have signed written informed consent. Efficacy assessment was done using the Positive and Negative Syndrome Scale PANSS, Clinical Global Impression of Severity (CGI-S), and Calgary Depression Symptom scale (CDSS). Ratings were performed on baseline (within 24 hours before the first application of study drug), at the end of the 7 and 28 days of treatment. Three patients dropped out from the study and their basal samples were therefore excluded: 2 patients required SSRI treatment, and 1 patient withdrew consent. The following adverse events were reported during the study period: insomnia (N=2), headache (N=3), agitation (N=2), and muscular rigidity (N=1). Blood samples (8 ml) were collected into plastic syringes with 2 ml of acid citrate dextrose anticoagulant at 08.00 h. The determination of the platelet 5-HT concentration was done in platelet rich plasma using spectrofluorimetric method, as previously described (Muck-Seler et al. 1999). The results were expressed as means ± SD. Statistical evaluation of the data was done using one-way analysis of variance (ANOVA), followed by the Tukey's multiple comparison test, and with multiple regression analysis. The level of significance was set at p=0.05.

Platelet 5-HT concentration did not differ significantly [$F(5, 57)= 0.298$, $p=0.912$] between 8 female and 13 male schizophrenic patients before, and after 7 and 28 days of ziprasidone treatment (Table 1). Multiple regression model was not significant ($R^2=0.183$; *adjusted* $R^2=-0.061$; $F(3,10)=0.749$; $p=0.547$), and revealed that platelet 5-HT concentration was not significantly correlated to gender ($t=0.441$, *Beta*=0.130, $p=0.669$), age ($t=-0.613$, *Beta*=-0.176, $p=0.554$), or smoking ($t=1.293$, *Beta*=0.385, $p= 0.225$). The treatment with ziprasidone significantly decreased total PANSS scores after 7 and 28 days of treatment [$F(2, 62)= 8.771$, $p=0.001$], and total CGI-S [$F(2, 62)= 6.002$, $p=0.002$], or CDS [$F(2, 62)= 6.787$, $p=0.002$] scores after 28 days of treatment with ziprasidone (data not shown).

To the best of our knowledge, no data on the effect of ziprasidone on platelet 5-HT concentration is yet available, and we have found the lack of effect of 7 and 28 days of treatment with ziprasidone (109 mg/day) on platelet 5-HT concentration in male of female schizophrenic patients. Ziprasidone treatment did not reduce platelet 5-HT concentration, and this finding might be explained by the suboptimal antidepressant dose of ziprasidone, although lower doses were also reported to be effective (Moeller et al. 2007), and the clinical effects of ziprasidone on symptoms of schizophrenia and depression were achieved with these lower doses (present study; Daniel el al. 1999). We could speculate that ziprasidone might have shown inhibitory effect on platelet 5-HT concentration if prescribed in higher doses (Daniel et al. 1999). Although ziprasidone has the highest potency for human 5-HTT (Kd=39 nM) among atypical antipsychotics, its Kd is substantially weaker than that of SSRI paroxetine (Kd=0.13 nM), (Tatsumi et al. 1999), which was reported to reduce platelet 5-HT concentration after 28 days of treatment in depressed patients (Muck-Seler et al. 2002). The explanation of the antidepressant effect of ziprasidone might be due to other mechanisms, such as noradrenalin and dopamine reuptake blocking properties (Tatsumi se al. 1999), or 5HT2A, 5HT2C and 5HT7 blocking properties (Schmidt et al. 2001; Stahl and Shayegan, 2007). Although gender (Muck-Seler et al. 1999), smoking and age (Nenadic Sviglin et al. 2011) significantly affected platelet 5-HT concentration in our previous studies, present study failed to detect significant effect of these variables on platelet 5-HT concentration. Limitations of the study are that patients receiving ziprasidone were not randomized, the number of included subjects was small, blood ziprasidone concentration was not measured and patient compliance was not checked. However, since all patients were hospitalized during the whole trial, ziprasidone intake was controlled by nurses.

In conclusion, ziprasidone did not significantly affect platelet 5-HT concentration in male and female schizophrenic patients. These findings strongly argue against our hypothesis that ziprasidone significantly affects 5-HT reuptake *in vivo*.

Authorship

All authors have made a significant contribution to the conception and design or the analysis and interpretation of data, have participated in drafting the article or reviewing and/or revising it for intellectual content, and have approved the final version of the manuscript.

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Table 1. Platelet 5-HT concentration in female and male schizophrenic patients before and after 7 and 28 days of treatment with ziprasidone. 5-HT= serotonin. Data are presented as means ± SD. Ziprasidone did not affect platelet 5-HT concentration

	Platelet 5-HT (nmol/mg p)		
Schizophrenic patients	At baseline	After 7 days	After 28 days
Male	1.01 ± 0.34	1.05 ± 0.36	1.00 ± 0.19
Female	1.04 ± 0.13	1.14 ± 0.43	0.98 ± 0.13