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ANTIPSYCHOTIC DRUGS DO NOT AFFECT PLATELET 5-HT CONCENTRATION IN SCHIZOPHRENIC PATIENTS

Abstract

Rationale: Although antipsychotic drugs are prescribed for the treatment of schizophrenia and psychotic disorders, some of these drugs are also reported to possess antidepressant properties. Therefore, they are more frequently used either as a monotherapy or as an addition to antidepressant medication treatment in depression.
Objectives: The data on the effects of antipsychotic drugs on serotonin (5-hydroxytryptamine, 5-HT) transporter (5-HTT) in vivo when given to patients in therapeutic doses are still scarce.
Methods: Patients with schizophrenia or schizoaffective disorders in both male and female patients, were treated with antipsychotic drugs: 25 patients received olanzapine (12.8 ± 2.8 mg/day), 14 patients were treated with typical antipsychotic, fluphenazine N=14 (10.5 ± 2.5 mg/day) and for comparison, 21 patients were treated with ziprasidone (109.0 ± 27.1 mg/day). Platelet 5-HT concentration was determined fluorimetrically and evaluated at baseline and after 28 days in 65 healthy control subjects and in 60 patients.
Results: Platelet 5-HT concentration did not differ significantly [$F(3, 246)=0.597$; $p=0.677$] between medication-free healthy control subjects sampled at baseline and after 28 days compared to schizophrenic patients sampled before and 28 days after antipsychotics. Tukey's multiple comparison test revealed that treatment with fluphenazine ($p=0.853$), olanzapine ($p=0.117$), or ziprasidone ($p=1.000$) did not significantly alter platelet 5-HT concentration after 28 days of treatment compared to their baseline values, i.e. values before treatment.
Conclusions: Although all antipsychotics used in the study possess some antidepressant effects that are assumed to be related to their serotonergic properties, and have been reported to have *in vitro* binding affinity for human 5-HTT, the present study failed to detect significant *in vivo* effects of typical (fluphenazine) or atypical (olanzapine, ziprasidone) antipsychotics on platelet 5-HT concentration in schizophrenic patients.

Keywords

• Olanzapine • Fluphenazine • Ziprasidone • Platelet serotonin • Schizophrenia

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1. Introduction

Atypical antipsychotic drugs have different, multireceptor-binding profile, compared to typical antipsychotics. They have relatively higher serotonergic 5-HT2A receptor affinity compared to the dopaminergic D2 receptors. The atypical antipsychotic drug olanzapine is a drug in the thienobenzodiazepine class. It is a potent antagonist of 5-HT2A and D1, D2 and D4 receptors, with a higher affinity for 5-HT2A than for D2 receptors [1,2]. Fluphenazine is a conventional antipsychotic that blocks D1 and D2 receptors [3], and has moderate affinity for 5-HT2 receptors [4] that diminish psychotic symptoms. Ziprasidone is also an atypical antipsychotic drug that has a unique multireceptor-binding profile with a high ratio of 5-HT2A/D2, 5-HT2C/D2 and 5-HT1A/D2 receptor binding [5-7]. Although antipsychotic drugs are prescribed for the treatment of schizophrenia and psychotic disorders, some of these drugs have been reported to possess antidepressant properties. This antidepressant efficacy has been used in treatment, either as monotherapy or as an addition to treatment with various antidepressant drugs [8,9]. There is a trend of increased prescription of these drugs in the treatment of depression [10]. The antidepressant properties of antipsychotic drugs may be due to the pharmacological blockade of serotonin (5-hydroxytryptamine, 5-HT) transport, which terminates the synaptic action of 5-HT by its reuptake. The binding potency to the 5-HT transporter (5-HTT) or the equilibrium dissociation constants (Kd) for human 5-HTT of ziprasidone, olanzapine and fluphenazine have been shown to differ significantly [11]. Namely, ziprasidone has a high binding affinity (Kd=39 nM), while fluphenazine has a moderate binding affinity (Kd=400 nM), and olanzapine has a low affinity (Kd=1310 nM) for human 5-HTT [11]. These data [11] suggest that some of these antipsychotic compounds might also bind, with varying binding potencies, to 5-HTT *in vivo*.

The antidepressant properties could be important additional advantages of antipsychotic drugs, since major depression is frequently associated with schizophrenia, and clinically significant depression was reported in more than 50% of patients with schizophrenia or schizoaffective disorders [12].

Platelet 5-HT concentration is assumed to represent a valid biomarker that can show the compliance of patients treated with selective serotonin reuptake inhibitors (SSRI), since all SSRIs block 5-HT transport and significantly decrease platelet 5-HT concentration [13-16]. A fall of platelet 5-HT concentration has been

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repeatedly found after treatment with SSRI [13-16]. The data on the effects of olanzapine or fluphenazine on 5-HTT *in vivo* when given to patients in therapeutic doses are still scarce. Recently it has been shown that ziprasidone does not affect 5-HTT *in vivo* when given to schizophrenic patients in lower (109 mg/day) doses [17] than those used for the treatment of schizophrenia. Namely, ziprasidone has been reported to be devoid of any effect on platelet 5-HT concentration in schizophrenic patients [17]. Since there is a lack of *in vivo* data on the effects of olanzapine and fluphenazine on 5-HT concentration in humans, and platelet 5-HT concentration is an easy obtainable biomarker that will be reduced if a drug blocks platelet 5-HTT, the aim of this study was to investigate the effect of the atypical antipsychotic olanzapine and the typical antipsychotic fluphenazine on platelet 5-HT concentration; and to compare these effects with the effect of ziprasidone, in patients with schizophrenia or schizoaffective disorders. We hypothesized that if these drugs affect human 5-HTT, schizophrenic patients treated with olanzapine or fluphenazine will have altered (i.e. decreased) platelet 5-HT concentration after 28 days of treatment, compared to baseline values.

2. Methods and materials

2.1 Subjects

Study group comprised of 60 patients, men and women, older than 18 years with the DSM-IV diagnosis of schizophrenia or schizoaffective disorders [18]. The diagnosis was attained using the Structured Clinical Interview based on DSM-IV criteria [19]. Patients were excluded if they had received ziprasidone, fluphenazine, olanzapine, SSRIs, tricyclic antidepressants or other drugs that affect serotonin uptake, in the previous four weeks. They were also excluded if they had recorded past adverse reactions to ziprasidone, fluphenazine, or olanzapine. Moreover, the study excluded those who had dementia or any other organic mental disorder, and substance abuse and dependence in the previous three months, with the exception of nicotine and caffeine dependence. Patients with abnormal ECG, those with a corrected (QTc) interval exceeding 450 ms, or those receiving concomitant drugs known to prolong QTc interval, were also excluded. The only drugs allowed during the study, besides monotherapy with olanzapine, fluphenazine or ziprasidone, were benzodiazepines, hypnotics, and anticholinergic drugs to treat extrapyramidal symptoms. There was no lower or upper limit for the Positive and Negative Syndrome Scale (PANSS) total scores [20]. However, severely psychotic patients were not recruited because they were supposed to require intramuscular antipsychotics or the combination of antipsychotics. Severely depressed patients, which required the addition of antidepressants, were also excluded.

The study design: 25 patients were treated with olanzapine (12.8 ± 2.8 mg/day), and 14 patients were treated with fluphenazine (10.5 ± 2.5 mg/day). For comparison purposes, these results were compared with data from 21 schizophrenic patients who were treated with ziprasidone (109.0 ± 27.1 mg/day) [17].

Healthy female medication-free volunteers (N=65) had no known prior or current psychiatric diagnoses. The study protocols were carried out in Department for Psychiatry, University Hospital Center Zagreb. The study was approved by the hospital review board and the Ethics Committee of the University Hospital Center Zagreb, and has therefore been performed in accordance with the ethical standards established by the 1964 Declaration of Helsinki. All subjects provided signed informed consent.

2.2 Determination of platelet 5-HT concentration

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 [21,22]. Platelet protein concentrations were measured by the method according to Lowry [23]. Sampling was repeated on the 28th day of treatment or after the first sampling in the control group.

2.3 Statistical analysis

Statistical evaluation of the results, expressed as means ± SD, was done using one-way analysis of variance (ANOVA) followed by a Tukey's multiple comparison test. The level of significance was set at p=0.05.

3. Results

Platelet 5-HT concentration did not differ significantly [$F(3, 246)=0.597$; $p=0.677$] between medication-free healthy control subjects sampled at baseline (1.18 ± 0.26) and after 28 days (1.16 ± 0.27) and between schizophrenic patients sampled before (1.25 ± 0.46) or 28 days after (1.21 ± 0.53) different antipsychotic drugs.

To evaluate the effect of 28 days of treatment with olanzapine or fluphenazine on platelet 5-HT concentration, platelet 5-HT concentration was determined at baseline and after 28 days in schizophrenic patients treated with olanzapine or fluphenazine, and for the comparison in healthy control subjects sampled at the same time. These results were compared with the results obtained after ziprasidone treatment (Figure 1). Although there were significant [$F(7, 242)=3.943$; $p<0.001$] differences in platelet 5-HT concentration among these groups, these differences were not induced by the antipsychotic treatment (Figure 1). Tukey's multiple comparison test revealed that treatment with olanzapine ($p=0.117$), fluphenazine ($p=0.853$) or ziprasidone ($p=1.000$) did not significantly alter platelet 5-HT concentration after 28 days of treatment compared to their baseline values, i.e. values before treatment. In addition, there was no significant difference between platelet 5-HT values in the healthy control group sampled at two time points ($p=0.602$). Platelet 5-HT concentration was significantly higher at baseline in patients treated with fluphenazine than in patients treated with ziprasidone ($p=0.003$). After 28 days of treatment, there were no significant ($p>0.05$) differences in platelet 5-HT concentration among all treatment groups (Figure 1). To confirm these results, one-way ANOVAs separately evaluated each group of patients treated with fluphenazine [$F(1, 26)=0.724$; $p=0.403$], olanzapine [$F(1, 48)=0.044$; $p=0.835$] or ziprasidone [$F(1, 40)=0.157$; $p=0.694$] at baseline and after 28 days of treatment. The results revealed no significant differences in platelet 5-HT concentration before and after treatment, and

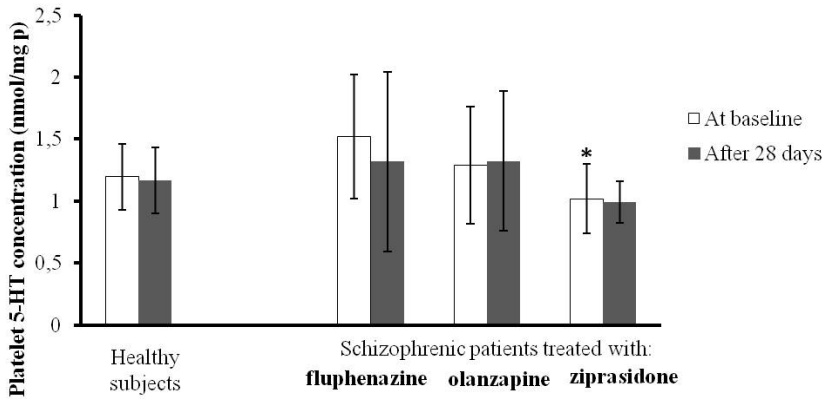

Figure 1. Platelet 5-HT concentration in healthy control subjects sampled two times and in schizophrenic patients before and after 28 days of treatment with fluphenazine, olanzapine and ziprasidone. Data are presented as means ± SD. 5-HT= serotonin. Fluphenazine, olanzapine or ziprasidone did not alter significantly platelet 5-HT concentration after 28 days when compared to baseline values. The only significant difference found was a higher baseline platelet 5-HT concentration in patients treated with fluphenazine than in patients treated with ziprasidone (asterisk).

confirmed that various antipsychotic drugs did not change platelet 5-HT concentration.

4. Discussion

The major finding of this study is the lack of effect of various antipsychotic drugs (olanzapine, fluphenazine or ziprasidone) on platelet 5-HT concentration. Similarly to our previous results, showing that ziprasidone (average dose of 109 mg/day) did not reduce platelet 5-HT concentration in schizophrenic patients [17], atypical antipsychotic olanzapine and neuroleptic fluphenazine did not decrease platelet 5-HT concentration. A recent study [24] showed no changes in mean platelet 5-HT content between acute psychiatric patients treated with secondary antipsychotics, lithium, neuroleptics and stabilizers, and our present and previous [17] results confirmed this finding. Although the present study included a small number of patients treated with olanzapine or fluphenazine (and in comparison with ziprasidone), if these antipsychotic drugs inhibit 5-HTT *in vivo*, their inhibitory effects would have been detectible in these groups of patients after 28 days of treatment.

The only significant difference found in the present study was a higher baseline platelet 5-HT concentration in patients treated with fluphenazine than in patients treated with ziprasidone. These higher platelet 5-HT values before treatment with fluphenazine might be induced by the presence of more positive symptoms of schizophrenia at baseline in fluphenazine than in ziprasiodone treated schizophrenic patients [25,26].

Treatment with olanzapine, as a monotherapy [27], or in combination with antidepressant drug such as fluoxetine [28], was effective in the treatment of patients with major depressive disorder or with bipolar depression, respectively. Clinical studies [29,30] have shown that the typical antispychotic fluphenazine improved depressive symptoms in patients with schizophrenia. The beneficial effect of fluphenazine on depressive symptoms was observed in female schizophrenic patients [30]. The efficacy of ziprasidone was reported as an add-on treatment in patients with treatment-resistant major depression [31-33], psychotic depression [34] and depression in schizoaffective disorder [12]. Ziprasidone was also shown to be effective as a monotherapy in a double-blind study, involving patients with schizoaffective disorder with prominent negative symptoms, although less effective than olanzapine [35].

Although *in vitro* binding affinity for human 5-HTT was moderate for fluphenazine (Kd=400 nM) and low for olanzapine (Kd=1310 nM), these data might suggest that some of the antidepressant properties might be achieved by the blockade of 5-HTT [11]. However, these binding properties were weaker than the binding properties of other antipsychotic compounds (such as triflupromazine, fluperlapine, chlorpromazine, and zotepine), who are relatively potent with Kd values in the range of 20 to 40 nM for human 5-HTT, and especially the binding affinity of the SSRI paroxetine (Kd=0.13 nM) [11]. Therefore, antipsychotic drugs used in this study did not have the potency to block in vivo 5-HTT, since their potencies were not sufficient to affect (*in vivo*) platelet 5-HT in female schizophrenic patients. Platelet 5-HT concentration was significantly reduced after 28 days of treatment with paroxetine (given in a dose of 20 mg daily) in either depressed [14] or bipolar depressed [16] patients, however, as opposed to fluphenazine, olanzapine or ziprasidone, its Kd for human 5-HTT is high [11]. Although only ziprasidone appears to have a Kd for human 5-HTT [11] similar to those of antidepressants imipramine and amitryptiline [36], its affinity for human 5-HTT was weak and therefore was not able to reduce platelet 5-HT concentration. Therefore fluphenazine, and olanzapine, similarly to ziprasidone [17], and other antipsychotics [24], were not able to reduce platelet 5-HT concentration *in vivo*.

In conclusion, although all antipsychotics used in the study were reported to possess some antidepressant effects that are assumed to be related to their serotonergic properties, the present and previous [17] results failed to detect significant effects of olanzapine, ziprasidone or fluphenazine on platelet 5-HT concentration in patients with schizophrenia or schizoaffective disorders.

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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Conflict of Interest

All authors declared no financial relationship with the Organization that sponsored the research, and have no conflict of interest. Authors state that they have full control of all primary data and they agree to allow the journal to review their data if requested.

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