The prognostic value of dopamine receptor occupancy by \([^{123}\text{I}]\)IBZM–SPECT in schizophrenic patients treated with quetiapine

László Pávics¹, György Szekeres², Edit Ambrus¹, Szabolcs Kéri², Zoltán Kovács², Miklós Árgyelán¹, Balázs Kanyó¹, László Csernay¹, Zoltán Janka²

¹Department of Nuclear Medicine, ²Department of Psychiatry University of Szeged, Szeged, Hungary

[Received 8 IV 2004; Accepted 9 IV 2004]

Abstract

BACKGROUND: In the present study D2 receptor occupancy was investigated in quetiapine treated schizophrenic patients for the detection of a relationship between the scintigraphic pattern and clinical signs and symptoms.

MATERIAL AND METHODS: In 10 schizophrenic patients \([^{123}\text{I}]\)IBZM–SPECTs were performed during the introduction of quetiapine therapy (600–800 mg/day) and during a lower maintenance dose (200–400 mg/day). The patients’ clinical follow-up was continued for 1 year. For the evaluation of SPECT images, visual interpretation was performed and striatum/occipital lobe (S/O) activity ratio was calculated.

RESULTS: The initial striatum/occipital ratio was significantly higher in patients with relapse compared to the others (1.86 ± 0.17, 1.53 ± 0.15, p < 0.01). The decreasing striatum/occipital ratio (increasing D2 receptor occupancy) on the 2nd SPECT was a predictive factor for the relapse.

CONCLUSIONS: D2 receptor occupancy and its changes during quetiapine therapy were related to the prognosis of the treatment efficacy.

Key words: schizophrenia, quetiapine, IBZM-SPECT, clinical follow-up

Introduction

New atypical antipsychotics are being employed for treating schizophrenic disorders. In comparison with other traditional neuroleptic substances, these drugs have a lower or no potential to induce extrapyramidal side effects and have a high clinical efficacy [1]. Several studies have shown that different antipsychotics with a different occupancy of several neuroreceptors have a clinically similar effect [2, 3].

The role of dopamine receptors in schizophrenia has been widely investigated. By the introduction of SPECT neuroreceptor agents it is possible to employ these investigations not only as research tool but also as clinical diagnostic test. The most commonly available dopamine receptor binding agent is the benzamide derivative \([^{123}\text{I}]\)IBZM \([(S)-2-hydroxy-3-iodo-6-methoxy-N-\{1-ethyl-2-pyrrolidinyl\}(methyl)benzamide]\) [4, 5]. The \([^{123}\text{I}]\)IBZM is a ligand to the postsynaptic receptors of the D2 receptor family. The involvement of postsynaptic D2 receptors in schizophrenia and the effect of different antipsychotics in relation to the clinical response, prognosis, and extrapyramidal side effects were investigated [6–9].

Quetiapine is relatively new atypical antipsychotic compound with a receptor profile differing from classical neuroleptics. Animal in vitro studies revealed an even lower affinity of quetiapine for D2 receptors than that of e.g. clozapine. Preclinical tests of quetiapine in animal experiments predicted antipsychotic activity and low extrapyramidal side effects [10]. In humans the D2 receptor occupancy rate with a 600–700 mg/day dose has been shown to be about 24–28% [11, 12]. According to the clinical investigations, an initial higher dose of quetiapine is recommended followed by a lower dose to maintain clinical steady state.

Correspondence to: László Pávics
Department of Nuclear Medicine, University of Szeged
H-6720 Szeged, Korányi fasor 8., Hungary
Tel: (+36 62) 54 53 90, fax: (+36 62) 54 45 64
e-mail: pavicsl@ss10.numed.szote.u-szeged.hu
The aim of our study was to investigate the D2 receptor occupancy by \[^{123}\text{I}\] IBZM-SPECT in patients treated with a high and later, with a low dose of quetiapine in relation to the long-term clinical response and detectable side effects.

Material and methods

Patients

Ten schizophrenic patients (7 women, 3 men, age ± SD: 34 ± 7, PANSS: 72 ± 20) were involved in the study. All subjects received a thorough psychiatric, medical and neurological evaluation, including a brain CT to rule out structural lesions. All subjects were diagnosed as schizophrenic according to DSM-IV criteria, and had been free of active medical problems or substance abuse during the previous 6 months. All subjects were chronically ill. All subjects were under hospital care during the period of SPECT investigation, in order to decrease the alteration of the patients’ condition due to different hydration and diet. The clinical data of the patients are summarised in Table 1.

Quetiapine monotherapy was introduced in a dose of 600–800 mg/day. After 2 months, the dosage of quetiapine was decreased to 200–400 mg/day. The clinical follow-up of the patients lasted for up to 1 year.

SPECT data acquisition

In each patient, 3 weeks after introduction of the treatment, \[^{123}\text{I}\] IBZM-SPECT investigations were performed, and the SPECT was repeated 3 weeks after the beginning of the lower dose of quetiapine. In all cases the last dose of quetiapine was taken in by the patients 2 hours before the SPECT investigation. According to previous experimental data, the maximum drug plasma concentration is 2–3 hours after an intake of quetiapine.

Clinical and neurological data were obtained on all subjects on the day of the IBZM-SPECT scan and thereafter monthly for one year. Clinical ratings included the Positive and Negative Syndrome Scale (PANSS). The extrapyramidal signs, parkinsonism and dyskinesia were assessed with the Simpson-Angus Scale (SAS), modified Abnormal Involuntary Movement Scale (AIMS) and by the Barnes Akathisia Scale (BAS). To receive a diagnosis of drug-induced parkinsonism, subjects were required to have an abnormal score on two of the three cardinal signs of the disorder (tremor, rigidity, bradykinesia).

During the SPECT procedure, 60 minutes after the oral administration of 450 mg potassium-perchlorate, the patient was given 185 MBq \[^{123}\text{I}\] IBZM (Cygne BV Holland) intravenously. The SPECT data acquisition was started 90 minutes after the IBZM injection. For this a rotating single head gamma camera with low energy high-resolution collimator (Siemens Diacam) connected to a computer system (Siemens Icon) was used. Data were collected for 120 projections (360° rotation) in 128 x 128 matrix. The acquisition times were 30 seconds per projection. Images were reconstructed by a filtered back projection using a Butterworth filter with a cut-off frequency of 0.5 Nyquist, power factor 10. The reconstructed images were corrected for gamma ray attenuation using the Chang method with an attenuation coefficient of 0.12 cm\(^{-1}\).

SPECT image analysis

The reconstructed slices were visually assessed by three well-trained observers and semi-quantitatively evaluated. The observers were blind to the medication status of the subject. In three consecutive transversal slices with the highest IBZM uptake at the level of striatum, striatum/occipital lobe activity ratios were calculated and averaged separately on the left and right side. The ratios were calculated using the ROI method. Elliptical ROIs were placed on the consecutive transversal slices at the level of basal ganglia with the highest uptake of the striatum. The regional size of the striatum and the regional size of the occipital lobe were 100 ± 20 pixels and 47 ± 6 pixels, respectively. Two independent nuclear medicine specialists tested the reproducibility of the method used for determining the ratio. The ratios calculated by the two evaluators were statistically not different (two tailed t-test) and correlated well (Pearson correlation \(p < 0.05\)).

For the evaluation of the experimental data, a statistical analysis was performed by using the two-tailed t-test and correlations were calculated by the Pearson method. The significance level was set at \(p < 0.01\).

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>PANSS</th>
<th>Interval to relapse</th>
<th>Quetiapine dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>First</td>
<td>Second</td>
<td>(weeks)</td>
</tr>
<tr>
<td>1</td>
<td>74</td>
<td>74</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>93</td>
<td>96</td>
<td>3</td>
</tr>
<tr>
<td>3</td>
<td>52</td>
<td>56</td>
<td>4</td>
</tr>
<tr>
<td>4</td>
<td>98</td>
<td>100</td>
<td>2</td>
</tr>
<tr>
<td>5</td>
<td>114</td>
<td>108</td>
<td>-6</td>
</tr>
<tr>
<td>6</td>
<td>53</td>
<td>55</td>
<td>2</td>
</tr>
<tr>
<td>7</td>
<td>67</td>
<td>46</td>
<td>-21</td>
</tr>
<tr>
<td>8</td>
<td>65</td>
<td>65</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>82</td>
<td>76</td>
<td>-6</td>
</tr>
<tr>
<td>10</td>
<td>64</td>
<td>55</td>
<td>-9</td>
</tr>
</tbody>
</table>

PANSS — Positive and Negative Syndrome Scale
Results

The results are summarised in Table 1–2. The PANSS score changes varied in a wide range (from –21 to +4) from the time point of the 1st to the 2nd SPECT investigations. The PANSS scores did not differ significantly comparing the results at the 1st with the ones at the 2nd SPECT (76 ± 23 vs. 73 ± 23). The SAS, AIMS, BAS scores remained actually unchanged. There were also no clinical signs or symptoms of parkinsonism. Within the 1-year clinical follow-up, a relapse of the symptoms was observed in 5 patients, but the other 5 patients remained symptom-free. The PANSS score changes were in the range of –21–+4.

The postsynaptic dopamine receptor activity was found to be suppressed at the 1st IBZM-SPECT investigation in 3 patients (patients no.: 1, 4, 9) and normal in 7 patients by the visual evaluation. In the 2nd investigation, contrary to decreasing the dose of quetiapine, the receptor occupancy increased in 4 (patients no.: 3, 5–7), was unchanged in 3 (patients no.: 2, 8, 10) and decreased in 3 patients visually. The quantitative evaluation resulted in individually different striatum/occipital ratios at the 1st and also at the 2nd investigation. The changes of the striatal IBZM uptake ranged from –27 to +35%. The average uptake values of IBZM statistically did not differ between the 1st and the 2nd investigation (1.70 ± 0.23 vs. 1.68 ± 0.12). In 5 subjects, the values of striatum/occipital ratio increased and in 5 persons it decreased during the lowering the dosage of quetiapine. In the 5 patients with increased D2 receptor occupancy, each patient showed a relapse of an acute schizophrenic episode which was not seen in patients with decreased receptor occupancy (Figures 1 and 2). The initial striatum/occipital ratio was significantly higher in patients with a relapse compared to the others (1.86 ± 0.17, 1.53 ± 0.15, p < 0.01). The D2 receptor occupancy changes correlated with the time interval until the relapse (p < 0.01), but not with the PANSS changes or with the initial IBZM uptake ratios.

Discussion

The investigation of dopamine receptors by SPECT has become widely available. Experience has been obtained predominantly with the D2 receptor group visualisation by [123I] IBZM-SPECT. One of the most intensively studied disorders investigated with the method has been Parkinson’s disease. Recently, several groups used the investigations for demonstrating and clarifying the status of D2 receptors in different psychiatric illnesses. In schizophrenic patients several groups have shown an abnormality in D2 receptors [6, 8, 13]. The dopaminergic activity was related to the clinical signs and symptoms [3]. Dopamine receptors are common targets of traditional and atypical antipsychotics for therapeutic action [2, 3, 9, 11, 14, 15]. Recent developments in molecular biology and neuroimaging have helped test the mechanism of the drug’s effect through in vivo receptor imaging techniques. Because of the high dopamine receptor density and such an advantageous visualisation by neuroimaging, striatal D2 receptor occupancy is the most commonly investigated effect of the antipsychotics. However, the relationship of therapeutic response and striatal receptor occupancy is not evident. The findings of several studies using different atypical antipsychotics for the treatment of schizophrenia were similar to ours regarding the relationship of D2 receptor occupancy measured by [123I] IBZM-SPECT and clinical effect [3, 11]. In conclusion, the same clinical response can be observed with different striatal D2 receptor activities. Contrary to the antipsychotic effect, the striatal dopamine receptor occupancy is closely related to the extrapyramidal side effects of these substances [16, 17]. Clozapine is one of the first atypical antipsychotic compounds exhibiting less occupancy for D2 receptors and a low propensity to induce extrapyramidal signs compared to the traditional neuroleptics [1]. However, clozapine bears a heightened risk of potentially fatal agranulocytosis, therefore novel antipsychotics were developed with the same clinical

Table 2. Results of the [123I]IBZM-SPECT investigations in schizophrenic patients treated with quetiapine

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Visual evaluation</th>
<th>Semiquantitative evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>D2 receptor occupancy</td>
<td>(striatum/occipital ratio)</td>
</tr>
<tr>
<td></td>
<td>First investigation</td>
<td>Second investigation</td>
</tr>
<tr>
<td></td>
<td>R</td>
<td>L</td>
</tr>
<tr>
<td>1.</td>
<td>decreased</td>
<td>decreasing</td>
</tr>
<tr>
<td>2.</td>
<td>normal</td>
<td>unchanged</td>
</tr>
<tr>
<td>3.*</td>
<td>normal</td>
<td>increasing</td>
</tr>
<tr>
<td>4.</td>
<td>decreased</td>
<td>decreasing</td>
</tr>
<tr>
<td>5.*</td>
<td>normal</td>
<td>increasing</td>
</tr>
<tr>
<td>6.*</td>
<td>normal</td>
<td>increasing</td>
</tr>
<tr>
<td>7.*</td>
<td>normal</td>
<td>increasing</td>
</tr>
<tr>
<td>8.*</td>
<td>normal</td>
<td>unchanged</td>
</tr>
<tr>
<td>9.</td>
<td>decreased</td>
<td>decreasing</td>
</tr>
<tr>
<td>10.</td>
<td>normal</td>
<td>unchanged</td>
</tr>
</tbody>
</table>

* patients with relapse
Nuclear Medicine Review 2004, Vol. 7, No. 2

characteristics but lower side effects. Quetiapine is a relatively new agent with a different receptor profile compared to the classical neuroleptics. In vitro studies revealed a low affinity to D2 receptors (even lower than clozapine), higher affinity for 5-HT2A and no affinity for D1 receptors [18]. We did not have an own control group in our investigations but the data were compared to the normal distribution from the literature [19]. In the majority of the cases, after the introduction of quetiapine treatment, the first [123I]IBZM-SPECT investigations showed a low striatal D2 receptor occupancy. During the observation period, in concordance with the low D2 receptor occupancy rates, in none of the patients was any EPS observed. Quetiapine has a relatively short plasma elimination half-life influencing the results of in vivo receptor measurements depending on the administration of the last dose of the respective drug [11]. In our study the patients took the drug 2 hours before the radiopharmaceutical administration and were investigated in the same order at the second SPECT as at the first one. Gefvert et al. has reported the maximum D2 receptor occupancy at 2 hours after quetiapine administration, similar to the timing of our investigations [20]. The patients studied were under quetiapine monotherapy and did not earlier receive any typical or atypical neuroleptic agent with a possible influence on the dopaminergic status measured.

Nevertheless, we have not found data in the literature in relation to the prognostic value of D2 receptor occupancy changes using different doses of antipsychotics. The different levels of D2

Figure 1. First [123I]IBZM-SPECT investigation of patient no. 7 treated with 600 mg quetiapine. Striatum/occipital ratio: 1.81.

Figure 2. Second [123I]IBZM-SPECT investigation of patient no. 7 treated with 200 mg quetiapine. Striatum/occipital ratio: 1.57.
receptor occupancy and receptor occupancy changes might be dependent on the individual dopaminergic status of the patients. In schizophrenia, the dysregulation of the dopamine system includes the lower level of tonic DA release and an exaggerated DA response to different stimuli, like stress and psychoactive substances [21, 22]. These subcortical anomalies show a relationship with structural and functional impairments of the dorsolateral prefrontal cortex [23]. This complex disturbance of regulation is specific to the active phases of the illness, including prodromal phase, psychotic states and subsequent relapses, which could last several months [24]. The patient with a stable state of illness does not exhibit this neurochemical feature. In the active phase, stimuli can elicit increased dopamine release in the striatum, leading to a decrease in the S/O ratio during [123I]-IBZM-SPECT investigation [25]. At the time of the 2nd investigation, all of our patients were in a clinically stable state. In patients showing symptoms of relapse during the follow-up phase, the persistent hyperresponsive state of the striatal dopaminergic system can explain the increase in receptor occupancy in spite of the decreased dose of antipsychotic medication, delineating a group of patients with a higher risk of relapse. Recently, several groups mention the importance of extrastrial actions of atypical antipsychotics [3, 26]. However, we measured only the striatal D2 receptor occupancy in our work. According to our results, the initial blockade of striatal D2 dopamine receptor activity and its changes might play a role in the efficacy of quetiapine treatment in schizophrenia. The prognostic value of the effects of these drugs on other receptors has to be further elucidated with new radiopharmaceuticals having a selective affinity for these functions.

References


www.nmr.viamedica.pl