Atypical Antipsychotics Do Not Reverse Prepulse Inhibition Deficits in Acutely Psychotic Schizophrenia

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OBJECTIVES: To investigate the effects of atypical antipsychotics on prepulse inhibition, startle response and habituation in acutely psychotic patients with schizophrenia, and investigate whether prepulse inhibition deficit improvements are a result of the direct impact of atypical antipsychotics or improvements in antipsychotic-related symptoms. METHODS: Prepulse inhibition, habituation and acoustic startle response were evaluated in healthy control subjects and patients with schizophrenia (either unmedicated with antipsychotics at the time of hospitalization or medicated with atypical antipsychotics for \( \geq 1 \) month before hospitalization). RESULTS: Data were analysed for 26 patients in the unmedicated group, 20 patients in the medicated group and 31 control subjects. Compared with controls, both medicated and unmedicated patients showed prepulse inhibition deficits; however, there were no significant differences between the two patient groups. Lower prepulse inhibition levels were correlated with higher levels of positive, negative, general and total scores on the Positive and Negative Syndrome Scale. CONCLUSIONS: These results suggest that effects of atypical antipsychotics on prepulse inhibition may not be evident when patients with schizophrenia are acutely symptomatic, and do not directly influence prepulse inhibition.

KEY WORDS: Atypical antipsychotics; Acutely psychotic schizophrenia; Prepulse inhibition; Startle response; Habituation

Introduction

Prepulse inhibition of the acoustic startle reflex offers a measure of sensorimotor gating.\(^1\)\(^ - \)\(^3\) It is defined as a reduction of the startle reflex due to the intense startling stimulus being preceded by a weaker nonstartling prepulse.\(^1\) According to the sensorimotor gating concept, prepulse inhibition is thought to regulate sensory input by filtering out irrelevant stimuli in order to prevent sensory information overflow and to allow for selective and efficient processing of relevant information.\(^4\) Habituation, which is another aspect of the behavioural plasticity of the startle response, is the decrement in magnitude of the startle response as a result of repeated presentation of the same stimulus during a session.\(^5\) Reduced habituation has also been interpreted to reflect impaired gating, which
might result in cognitive disruption by sensory overload.\textsuperscript{6,7} Sensorimotor gating is influenced by factors such as sex, age and smoking status.\textsuperscript{8 - 10}

Prepulse inhibition deficits have been consistently demonstrated in schizophrenia.\textsuperscript{1,3,11 - 14} Moreover, it has also been reported that several measures of the startle response are influenced by atypical antipsychotics. A number of cross-sectional studies have found a normal prepulse inhibition range in patients treated effectively with atypical antipsychotics, but noted deficient prepulse inhibition in groups treated with typical antipsychotics. It has been reported that prepulse inhibition is intact in patients receiving atypical antipsychotics but deficient in patients receiving typical antipsychotics.\textsuperscript{15} Swerdlow \textit{et al.}\textsuperscript{16} found that the atypical antipsychotic quetiapine significantly enhanced prepulse inhibition at short prepulse intervals (20 – 30 ms) in ‘low gating’ humans. In another study, higher prepulse inhibition levels were found in patients treated with atypical antipsychotics compared with untreated patients and those taking typical antipsychotics.\textsuperscript{17} Similarly, it has been reported that patients with schizophrenia given typical antipsychotics, but not those given atypical antipsychotics, show reduced prepulse inhibition compared with healthy controls.\textsuperscript{11}

Generally, protocols compare patients before and after they have been given a drug. Even though findings support the position that atypical antipsychotics mediate prepulse inhibition, most studies have compared stable patients with low psychosis rating scores with more acutely psychotic patients, with high psychosis rating scores.\textsuperscript{13} Deficient prepulse inhibition has been found to be correlated with both positive and negative symptoms of schizophrenia.\textsuperscript{18} Thus, it is unclear whether prepulse inhibition deficit improvements are the result of direct impacts of atypical antipsychotics, or of improvements in patients’ antipsychotic-related symptoms. In order to clarify this issue, the present study assessed prepulse inhibition, startle response and habituation in healthy control subjects and in patients with schizophrenia who were hospitalized as a result of acute psychosis. Patients with schizophrenia were divided into two groups: those who were unmedicated with antipsychotics at the time of admission and remained unmedicated during the assessments; those who had received atypical antipsychotic medication for ≥ 1 month prior to admission and remained on medication during the assessments.

**Patients and methods**

**STUDY POPULATION**

Patients with schizophrenia who attended the Department of Psychiatry at Xijing Hospital, Xi’an, Shaanxi Province, China and were hospitalized (for a period of time) between April 2011 and October 2011, were included in the study; patients were enrolled into the study sequentially. For each patient, a consensus diagnosis of schizophrenia was made by at least two psychiatrists, according to the \textit{Diagnostic and Statistical Manual of Mental Disorders}, 4th edn, text revision (DSM-IV-TR\textsuperscript{®}),\textsuperscript{19} using the \textit{Structured Clinical Interview for DSM-IV-TR Axis I Disorders}.\textsuperscript{20} Patients were excluded if they were determined to have an additional axis I diagnosis, met the DSM-IV-TR\textsuperscript{®} criteria for substance abuse or dependence, or had a history of a neurological disorder (e.g. a head injury with loss of consciousness, organic psychosis or epilepsy). Patients were also excluded if they had a difficulty in hearing or had used benzodiazepines within the previous 24 h, either of which may affect the acoustic startle response.\textsuperscript{21,22}
Patients with schizophrenia were allocated into one of two groups according to their medication status at hospitalization. One group of patients reported that they had not taken antipsychotic medication for $\geq 1$ month prior to hospital admission: these patients remained free of antipsychotic medication until after they had been tested for prepulse inhibition, habituation and acoustic startle response (unmedicated group). The other group of patients reported that they had been taking atypical antipsychotic medication for $\geq 1$ month prior to hospitalization: these patients continued to receive atypical antipsychotic medication at the time of prepulse inhibition, habituation and acoustic startle response testing (medicated group). Hospital research staff verified patients’ medication status with patients’ family members. All patients included in the study were tested for prepulse inhibition, habituation and acoustic startle response within 24 h of being admitted to the Department of Psychiatry.

In addition, healthy subjects were tested for comparative purposes (control group). These subjects were recruited from the staff of the Department of Psychiatry or were husbands or wives of patients. These control subjects were interviewed to establish their mental health status. Individuals who had prior mental health problems or a family history of psychosis were excluded from the study.

All study participants were required to refrain from smoking cigarettes for $\geq 1$ h prior to testing, because nicotine has been reported to affect prepulse inhibition.\textsuperscript{17,23} The study was approved by the Xijing Hospital Ethics Committee, Xijing Hospital, The Fourth Military Medical University, Xi’an, Shanxi Province, China. After a complete description of the study was given to participants, written informed consent was obtained from them.

**STUDY PROCEDURES**

Patients with schizophrenia were assessed using the Positive and Negative Syndrome Scale (PANSS).\textsuperscript{24} The startle reflex to an acoustic stimuli was measured using Human Startle Software V 7.300-00 (Coulbourn Instruments, Allentown, PA, USA) and a physiological data acquisitions system (LaBlinc V system V15-17; Coulbourn Instruments). The tests were performed in a quiet room, with each participant seated comfortably in a soft chair. Participants were asked to remove watches and mobile phones in order to avoid electromagnetic interference, and were instructed to relax, stay awake and look at a red piece of paper on a white wall approximately 3 m in front of them. They were instructed to keep their eyes open as wide as possible. After cleaning the skin surface with 75% alcohol, silver/silver chloride electrodes (V91-02 Reusable Electrodes 4 mm [silver chloride]; Coulbourn Instruments) were positioned using high-conductivity microlyte electrolyte gel paste (Coulbourn Instruments, Whitehall, PA, USA) over and lateral to the orbicularis of the right eye (one electrode just under the lateral canthus; the other about 1 cm lower and medial to the pupil). A ground electrode was placed behind the right ear over the mastoid (V91-01 reusable 8 mm electrode [silver chloride]; Coulbourn Instruments); the skin cleaning and ground electrode fixing procedures were the same as for the electrodes placed near the eye. White noise of 70 dB was presented as a background noise, which started 5 min before the startle session began and was continuously present throughout the session. Acoustic startle stimuli were presented while the white noise was delivered via headphones.

Each trial consisted of three blocks. In the first and third blocks, the startle response to pulse alone was recorded eight times (sound
pressure, 110 dB; duration, 40 ms) to measure startle habituation. In the second block, the startle session consisted of 50 trials, with five conditions: a 110 dB white noise burst of 40 ms (pulse alone) and the same burst preceded 30, 60, 120 or 240 ms earlier by a prepulse of 40 ms of 86 dB; these conditions were presented in a pseudorandomized order.

The intertrial interval averaged 15 s (range 12 – 18 s) and each session lasted for approximately 17 min. The electromyographic (EMG) eye-blink component and the largest EMG value detected in the 20 – 150 ms following the onset of a pulse were measured and analysed by the human startle reflex software. EMG settings for the low- and high-pass filters were 150 Hz and 8 Hz, respectively.

STATISTICAL ANALYSES
Statistical evaluation of the data was carried out using the SPSS® statistical package, version 16.0 (SPSS Inc., Chicago, IL, USA) for Windows®. One-way analysis of variance (ANOVA) was used for between-group comparisons for age, education, age at illness onset, and PANSS (total, positive symptom, negative symptom and general psychopathology) scores. The acoustic startle response was assessed using data obtained in the first block of trials (pulse-alone trials). Group differences in acoustic startle response were assessed by applying a one-way ANOVA. Prepulse inhibition was calculated for the second block as the percentage decrease in startle magnitude in the presence of a prepulse, compared with the magnitude without a prepulse (1 – [prepulse amplitude/pulse amplitude] × 100%). Data were inspected for homogeneity and normality to determine whether a Kruskal–Wallis test/Mann–Whitney U-test (for pairwise comparison), or a one-way ANOVA repeated measures approach was most appropriate. Normality was tested by skewness and homogeneity by Levene’s test. Habituation of the startle response was measured by assessing the decrease in magnitude of the startle response to pulse-alone trials ([1 – mean startle magnitude in block 3/mean startle magnitude in block 1] × 100%). To assess group differences in habituation, one-way ANOVA was used. Spearman’s rank-order correlation analysis was used to evaluate the association of prepulse inhibition at the four prepulse conditions (30, 60, 120 and 240 ms) with PANSS scores for the entire group of patients with schizophrenia. Spearman’s rank-order correlation analysis also was used to evaluate the correlation between prepulse inhibition and first episode or recurrence. A P-value < 0.05 was considered statistically significant.

Results
In total, 52 patients with schizophrenia were included in the study: 28 patients in the unmedicated group; 24 patients in the medicated group. Some patients were excluded from the final analysis because they either had a lack of measurable startle response (mean amplitude in block 1 < 10 digital units) or they blinked too frequently and continuously, which meant that they could not meet the requirement of keeping their eyes open as wide as possible. In total, two patients in the unmedicated group and four patients in the medicated group were excluded. The final analysis included data for 26 patients in the unmedicated group (10 males and 16 females) and 20 patients in the medicated group (eight males and 12 females). In the unmedicated group, 15 patients were undergoing a first episode compared with none in the medicated group. There were 31 healthy subjects included in the control group (14 males and 17 females). All patients and controls were of Han ethnicity.
Demographic and clinical characteristics of the study participants are shown in Table 1. There was a significant difference among the three groups for years of education: the control group had the longest time in education compared with the patients with schizophrenia \((P = 0.023, \text{versus medicated and unmedicated groups, combined})\). There were no significant differences in age and sex distribution among the three groups.

When the two groups of patients with schizophrenia were compared there were no statistically significant differences in age, years of education or age at onset of illness. There were only two cigarette smokers in the unmedicated group, one in the medicated group and four in the control group, with no statistically significant differences in smoking status between the groups. Patients in the unmedicated group had significantly higher PANSS total, positive and general scores compared with those in the medicated group \((P = 0.003, P < 0.001 \text{and} P = 0.003, \text{respectively}; \text{Table 1})\).

In the medicated group, patients were recorded as having received the following therapies: risperidone \((n = 5)\), clozapine \((n = 2)\), olanzapine \((n = 6)\), aripiprazole \((n = 1)\), ziprasidone \((n = 1)\), paliperidone \((n = 2)\), quetiapine \((n = 1)\) or a combination therapy of risperidone and olanzapine \((n = 2)\).

The mean ± SD acoustic startle response and habituation for the unmedicated, medicated and control groups are shown in Table 1. There were no statistically significant differences in these parameters between the three groups.

The normality and homogeneity of the prepulse inhibition data were examined and it was found that there was a highly skewed distribution of scores (range –1 to –3) as well as a heterogeneous variance among the groups. Thus, the Kruskal–Wallis test was selected to analyse the data.

The median prepulse inhibition values for the three groups are shown in Fig. 1. There

### Table 1: Demographic characteristics, clinical characteristics, acoustic startle response and habituation for healthy subjects (control group) and patients with schizophrenia who had not, or had, been taking antipsychotic medication for ≥1 month prior to hospitalization (unmedicated group and medicated groups, respectively)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Unmedicated group ((n = 26))</th>
<th>Medicated group ((n = 20))</th>
<th>Control group ((n = 31))</th>
<th>Statistical significance(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>24.50 ± 4.43</td>
<td>24.30 ± 5.09</td>
<td>26.29 ± 6.50</td>
<td>NS</td>
</tr>
<tr>
<td>Education, years</td>
<td>13.11 ± 2.83</td>
<td>12.55 ± 2.80</td>
<td>14.61 ± 2.62</td>
<td>(P = 0.023)(^b)</td>
</tr>
<tr>
<td>Age at illness onset, years</td>
<td>22.27 ± 3.57</td>
<td>21.85 ± 4.79</td>
<td>NA</td>
<td>NS</td>
</tr>
<tr>
<td>PANSS</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NS</td>
</tr>
<tr>
<td>Positive</td>
<td>24.54 ± 5.70</td>
<td>16.95 ± 4.78</td>
<td>–</td>
<td>(P &lt; 0.001)</td>
</tr>
<tr>
<td>Negative</td>
<td>18.58 ± 7.29</td>
<td>21.40 ± 6.24</td>
<td>–</td>
<td>NS</td>
</tr>
<tr>
<td>General</td>
<td>48.69 ± 7.23</td>
<td>41.85 ± 7.12</td>
<td>–</td>
<td>(P = 0.003)</td>
</tr>
<tr>
<td>Total</td>
<td>91.81 ± 11.16</td>
<td>80.20 ± 13.97</td>
<td>–</td>
<td>(P = 0.003)</td>
</tr>
<tr>
<td>Acoustic startle response, %</td>
<td>56.88 ± 32.92</td>
<td>73.06 ± 35.51</td>
<td>73.01 ± 48.84</td>
<td>NS</td>
</tr>
<tr>
<td>Habituation, %</td>
<td>34.80 ± 39.25</td>
<td>36.80 ± 33.88</td>
<td>39.25 ± 31.13</td>
<td>NS</td>
</tr>
</tbody>
</table>

Data presented as mean ± SD.

\(^a\)One-way analysis of variance.

\(^b\)Control group versus medicated and unmedicated groups, combined.

PANSS, Positive and Negative Syndrome Scale; NA, not applicable; NS, not statistically significant \((P \geq 0.05)\).
was a significant difference in rankings between the control group and patients with schizophrenia for the 30 ms prepulse condition \( (P = 0.011) \) and the 120 ms prepulse condition \( (P = 0.020) \). There were no statistically significant differences in rankings for the 60 ms and 240 ms prepulse conditions among the three groups.

Follow-up comparisons using the Mann–Whitney \( U \)-test indicated that patients in the unmedicated group had significantly different prepulse inhibition levels compared with the control group for the 30 ms prepulse condition \( (P = 0.006) \) and the 120 ms prepulse condition \( (P = 0.029) \). Patients in the medicated group had significantly different prepulse inhibition levels compared with the control group for the 30 ms prepulse condition \( (P = 0.027) \) and the 120 ms prepulse condition \( (P = 0.014) \). There were no statistically significant differences between the medicated and unmedicated patient groups at the four prepulse conditions tested (30 ms, 60 ms, 120 ms and 240 ms).

Spearman’s rank-order correlation analyses showed that there were significant inverse associations between PANSS positive scores and prepulse inhibition levels at the 30 ms prepulse condition \( (P = 0.031) \). The prepulse inhibition at the 120 ms prepulse condition was inversely correlated with the PANSS negative scores \( (P = 0.025) \), general psychopathology scores \( (P = 0.036) \) and total scores \( (P = 0.017) \). However, Spearman’s rank-order correlation analyses showed no significant correlation between prepulse inhibition and first episode or recurrence.

**Discussion**

The present study indicated that, on the measures of acoustic startle response, prepulse inhibition and habituation, there were no statistically significant differences between patients with schizophrenia presenting with acute psychosis who were unmedicated with antipsychotics at the time of hospitalization admission and those who had received atypical antipsychotics for \( \geq 1 \) month prior to hospitalization; those in the medicated group had been taking atypical antipsychotic medication for \( \geq 1 \) month prior to hospitalization. *\( P < 0.05 \) compared with healthy control subjects (Mann–Whitney \( U \)-test).
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month prior to admission. The results also agreed with previous studies that demonstrated prepulse inhibition deficits among patients with schizophrenia compared with healthy control subjects.1,6,11,25,26 There were no significant differences between the three groups in the present study, in terms of the acoustic startle response or habituation. However, for patients with schizophrenia, inverse correlations were found between PANSS total, positive, negative and general psychopathology scores and prepulse inhibition. In contrast to the present study, others have found that atypical antipsychotics could improve prepulse inhibition deficits in patients with schizophrenia. At 12 weeks after switching from the typical antipsychotic zuclopenthixol to the long-acting injectable atypical antipsychotic risperidone, patients with schizophrenia showed significant improvements in prepulse inhibition.27 After 6 months’ treatment with the atypical antipsychotic quetiapine, prepulse inhibition deficits in patients with schizophrenia were normalized to levels not statistically different from those in control subjects.13 Treatment for 8 weeks with the atypical antipsychotic olanzapine effectively increased prepulse inhibition levels in patients with schizophrenia, whereas treatment with risperidone or the typical antipsychotic haloperidol did not increase prepulse inhibition levels.28 In the above-mentioned studies, however, patients with schizophrenia exhibited symptom improvements after treatment. Thus, the improvements in symptoms may contribute to the restorative effects of atypical antipsychotics on prepulse inhibition. Based on these data, it remains unclear whether the observed prepulse inhibition deficit improvements are as a result of a direct pharmacological impact of atypical antipsychotics or because of a reduction in schizophrenic symptoms.

Lower levels of prepulse inhibition were correlated with higher levels of positive, negative, general psychopathology and total scores in the present study. One study tested 51 male patients with schizophrenia and found a correlation between prepulse inhibition deficits and both positive and negative symptoms of schizophrenia.18 Martinez-Gras et al.27 reported that long-acting risperidone improved prepulse inhibition deficits in patients with chronic schizophrenia and suggested that the prepulse inhibition-restoring effect of risperidone may be related to improvements in PANSS general psychopathology subscale scores. In acutely psychotic patients with schizophrenia, no statistically significant differences between patients who were unmedicated at the time of hospital admission and those who had been receiving medication for ≥1 week prior to admission was found, in terms of the impact on measures of startle magnitude, prepulse inhibition, or startle habituation.12 In contrast to that study, patients who took first-generation antipsychotics were excluded from the present study, as there is a view that atypical antipsychotics may be more effective at improving prepulse inhibition deficits than typical antipsychotics.15,16,27,29 In addition, the minimum medication period for patients in the present study was 1 month with antipsychotics, compared with 1 week in the study by Perry et al.12 The present study excluded patients who took benzodiazepines, in order to reduce interference from this class of drugs and to provide better differentiation of the effects of atypical antipsychotics on prepulse inhibition. The present study provides further understanding of previous data12 and...
indicates that atypical antipsychotics are of little direct significance in the improvement of prepulse inhibition deficits.

There were several limitations to the present study. Most importantly, for patients in the medicated group, recurrence of acute psychosis occurred either during a period when they were on maintenance therapy or when they had voluntarily reduced their medication dosage; there is a certain symptom recurrence rate under maintenance drug doses.30 Another important factor for symptom recurrence is that many patients (as well as their family members) lack an understanding of standardized medical treatments and the effects of a decrease in antipsychotic dosage or voluntary withdrawal from therapy. Consequently, dose may also be regarded as one of the important factors that affect prepulse inhibition. Notably, in the present study, patients’ plasma concentrations of atypical antipsychotic medications were not evaluated. In the unmedicated group, 15 patients were undergoing a first episode, whereas none were in the atypical antipsychotic medicated group. Spearman’s rank-order correlation analyses showed that there was no significant correlation between prepulse inhibition and first episode or recurrence.

The present study supports a view that, during acute psychotic states, no matter whether or not atypical antipsychotic medications are taken, prepulse inhibition will not be affected. In other words, in either circumstance, the neurobiological substrates underlying prepulse inhibition deficits may be dysregulated during acute psychotic states. Thus, the results suggest that atypical antipsychotic medication did not have a direct influence on prepulse inhibition.

In conclusion, the present study adds to the literature on information processing and suggests that prepulse inhibition is not directly affected by atypical antipsychotic medications when patients are acutely psychotic. Furthermore, the results indicate an inverse correlation between positive, negative, general psychopathology and total scores, and prepulse inhibition. These results suggest that the neurobiological substrates underlying prepulse inhibition deficits may be dysregulated during acute psychotic states, regardless of whether or not patients take atypical antipsychotics.

Conflicts of interest
The authors had no conflicts of interest to declare in relation to this article.
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