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Clozapine responders may have fewer extrapyramidal symptoms than non-responders: a preliminary report

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ABSTRACT

Purpose: Clozapine has been reported to be effective for refractory schizophrenic patients. However, there have been few reports investigating whether clozapine responders are likely to suffer from more or fewer extrapyramidal symptoms. The aim of the present study is to investigate the association between clinical effects of clozapine and extrapyramidal symptoms in clozapine-treated patients.
Methods: Ten patients were divided into Improvement Group with CGI-I scores ranging from 1 to 3 and Non-improvement Group with CGI-I scores ranging from 4 to 7. The Drug-Induced Extrapyramidal Symptoms Scale (DIEPSS) scores were compared between these two groups just before starting clozapine treatment and after 12 weeks of clozapine treatment.
Results: Although there was no significant difference in any DIEPSS scores between Improvement Group and Non-improvement Group just before clozapine treatment, Improvement Group had significantly fewer extrapyramidal symptoms in DIEPSS scores than Non-improvement Group after 12 weeks of clozapine treatment. Moreover, there was a significant interaction between overall severity of extrapyramidal symptoms assessed by DIEPSS and improvement measured by CGI-I across the 12 weeks of clozapine treatment.
Discussion: These findings suggest that clozapine responders are less likely to suffer from extrapyramidal symptoms.

Keywords: clozapine, CGI-I, DIEPSS, responders, extrapyramidal symptoms

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INTRODUCTION

Clozapine, the first of the second-generation antipsychotic drugs, was introduced into clinical practice in the beginning of the 1970s and was found to exert an antipsychotic effect with minimal extrapyramidal side effects in schizophrenic patients when given at the usual therapeutic doses of 300 to 600 mg/day. An analysis of 150 double-blind studies with 21,533 participants showed that clozapine had better overall efficacy than first-generation antipsychotic drugs and that clozapine induced fewer extrapyramidal side-effects than haloperidol [1]. In addition, a meta-analysis of 78 studies with 13,558 participants reported that clozapine was not significantly different from olanzapine, quetiapine, risperidone, and ziprasidone, and that clozapine was significantly more efficacious than zotepine [2].
The use of clozapine is restricted to refractory patients because of the risk of agranulocytosis, seizures, constipation, sedation, postural hypotension, myocarditis, and pancreatitis; in fact, extrapyramidal symptoms preclude the use and/or dose escalation of clozapine. With regard to extrapyramidal symptoms,

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Rummel-Kluge et al. [3] showed that clozapine induced significantly less use of antiparkinson medications than risperidone and zotepine; however, no difference was found between clozapine and olanzapine or ziprasidone.

With regard to the characteristics of clozapine responders, Nielsen et al. [4] revealed that a lower number of psychiatric hospitalizations and antipsychotic trials before clozapine initiation was a predictor of better response to clozapine, and Umbricht et al. [5] showed that clozapine responders exhibited fewer extrapyramidal symptoms at baseline than non-responders. To our knowledge, however, there have been few reports investigating whether clozapine responders are likely to suffer from more or fewer extrapyramidal symptoms during clozapine treatment, which may be important because if clozapine responders have fewer extrapyramidal symptoms they can continue to receive clozapine, but if they experience a higher number of more severe extrapyramidal symptoms they may discontinue clozapine. In the present preliminary study, we investigated the association between the clinical effects and extrapyramidal symptoms in clozapine-treated patients.

METHODS

Subjects

The subjects were 10 patients (7 female and 3 male) who consecutively admitted to our psychiatric ward from June 2010 to October 2011 and received clozapine therapy. As shown in Table 1, they were relatively young, with a mean age of 28.70 ± 7.10 years. All of them were diagnosed as suffering from schizophrenia (7 paranoid type, 3 disorganized type) according to DSM-IV-TR. They were resistant to at least two types of antipsychotic drugs (more than or equal to 600 mg/day of chlorpromazine equivalents for at least 4 weeks) and had received 4 to 16 antipsychotic drugs prior to admission. Moreover, several patients had taken antiparkinson drugs (Table 1). After admission, the patients were started on clozapine 12.5 mg/day, and the dose was gradually increased while the other antipsychotic drugs were gradually tapered off over 1 month. This resulted in all the patients being successfully switched to clozapine, with a mean maximum clozapine dose of 502.50 ± 97.50 mg/day. The IRB of Oita University Faculty of Medicine approved the use of clozapine and the use of the patients' data for the study, and informed consent was received from all patients.

Data Collection

The effect of clozapine was rated according to Clinical Global Impression-Improvement (CGI-I) scale for the state at 12 weeks of clozapine treatment compared to the state just before clozapine switching from other antipsychotic drugs. The CGI-I scale is a 7-point scale requiring the clinician to assess how much the patient's illness has improved or worsened; as the grades are: 1. Very much improved; 2. Much improved; 3. Minimally improved; 4. No change; 5. Minimally worse; 6. Much worse; and 7. Very much worse. Extrapyramidal symptoms were rated using Drug-Induced Extrapyramidal Symptoms Scale (DIEPSS) just before switching and just after 12 weeks of clozapine treatment. This scale is based on nine items (gait, bradykinesia, sialorrhea, rigidity, tremor, akathisia, dystonia, dyskinesia, and overall severity) rated from 0 to 4, with higher scores indicating more severe symptoms.

Statistical Analyses

The ten patients were divided into Improvement Group with CGI-I scores ranging from 1 to 3 and Non-improvement Group with CGI-I scores ranging from 4 to 7 after 12 weeks of clozapine treatment. The demographic data of the two groups are shown in Tables 1 and 2; no significant differences were found. The DIEPSS scores were compared between these two groups just before and after 12 weeks of clozapine treatment. Student's unpaired t-test and Fisher's exact probability test were used. If necessary, analysis of variance was also used.

RESULTS

As shown in Table 3, there was no significant difference in any DIEPSS scores between Improvement Group and Non-improvement Group just before clozapine treatment. Antipsychotic doses (chlorpromazine equivalents) were not significantly different (1303.67 ± 396.26 mg/day for patients in Improvement Group vs. 1043.75 ± 359.62 mg/day for patients in Non-improvement Group). As shown in Table 4, however, significant differences were found in DIEPSS scores, including the scores for bradykinesia, sialorrhea, tremor, and overall severity, after 12 weeks of clozapine treatment between the groups, even though there was no significant difference in clozapine or biperiden equivalent doses after 12 weeks between the groups (Table 2). Figure 1 shows that there was a significant interaction between DIEPSS overall severity and improvement in CGI-I

(F = 8.26, p = 0.021), and Figure 2 shows that there was a significant tendency of interaction between the biperiden equivalent dose and improvement in CGI-I (F = 4.68, p = 0.063).

Table 1. Patient Demographics and Antipsychotic Treatment Just Before Clozapine Treatment

Case	Age	Gender	Subtype	Antipsychotic drugs (mg/day)	Chlor-promazine e.q. (mg/day)	Anti-parkinson drugs just before clozapine treatment (biperiden e.q.; mg/day)
1	17	female	paranoid	perospirone (48) fluphenazine (8)	1,000	2
2	27	male	paranoid	blonanserin (24) zotepine (450) perphenazine (48)	1,762	2.5
3	33	male	disorganized	zotepine (525) risperidone (7) levomepromazine (200)	1,695	3
4	31	female	disorganized	haloperidol (24)	1,200	6
5	21	male	paranoid	olanzapine (20) blonanserin (24) levomepromazine (15)	1,415	0
6	30	female	paranoid	blonanserin (24) haloperidol (3)	750	2
7	30	female	paranoid	blonanserin (24) paliperidone (12) levomepromazine (75)	1,475	1
8	42	female	paranoid	aripiprazole (24)	600	0
9	33	female	paranoid	paliperidone (12) olanzapine (5)	1,000	0
10	23	female	paranoid	paliperidone (12) propericiazine (60)	1,100	0

Table 2. Patient Demographics of Improvement Group and Non-improvement Group After 12 Weeks of Clozapine Treatment

	Improvement Group	Non-improvement Group	*p*
Gender	F = 3, M = 3	F = 4, M = 0	0.20
Age	26.50 ± 6.25	32.00 ± 7.87	0.26
Subtype of schizophrenia	paranoid = 4 disorganized = 2	paranoid = 4	0.47
Maximum dose of clozapine (mg/day)	500.00 ± 83.67	506.25 ± 129.70	0.93
Antiparkinson drugs after 12 weeks of clozapine (biperiden e.q.; mg/day)	0.50 ± 1.23	1.00 ± 1.16	0.54

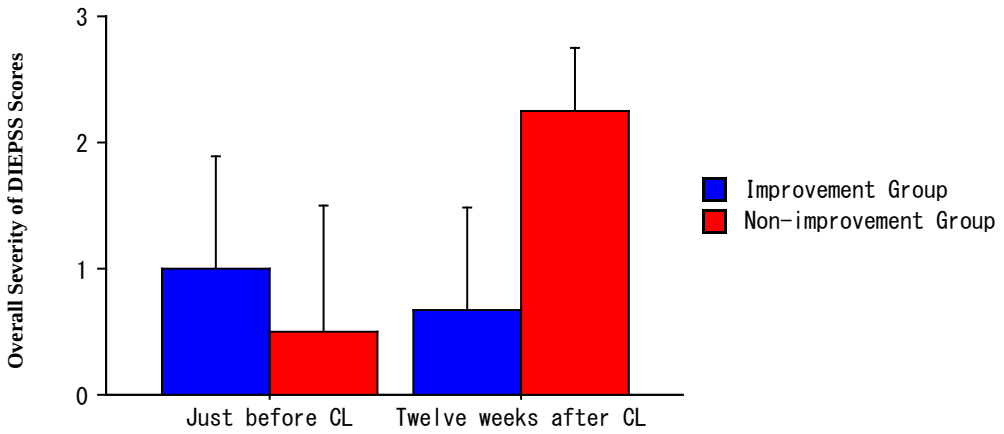
Ten patients were divided into Improvement Group with CGI-I scores ranging from 1 to 3 and Non-improvement Group with CGI-I scores ranging from 4 to 7.

Table 3. DIEPSS Scores of Improvement Group and Non-improvement Group Just Before Clozapine Treatment

	Improvement Group	Non-improvement Group	*p*
Gait	1.00 ± 1.10	0.50 ± 1.00	0.49
Bradykinesia	0.83 ± 0.98	0.75 ± 0.96	0.90
Sialorrhea	0.67 ± 0.82	0.50 ± 1.00	0.78
Rigidity	0.17 ± 0.41	0.00 ± 0.00	0.45
Tremor	0.17 ± 0.41	0.25 ± 0.50	0.78
Akathisia	0.00 ± 0.00	0.25 ± 0.50	0.25
Dystonia	0.00 ± 0.00	0.00 ± 0.00	
Dyskinesia	0.00 ± 0.00	0.00 ± 0.00	
Overall severity	1.00 ± 0.89	0.50 ± 1.00	0.44

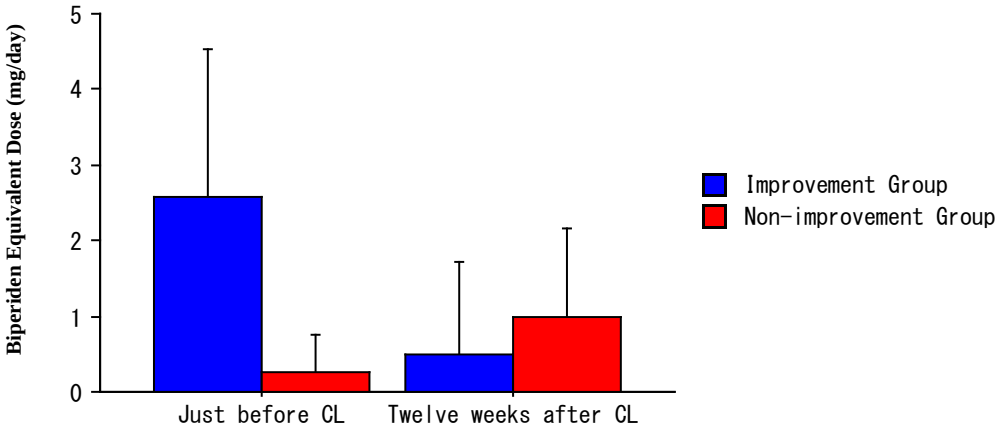
Table 4. DIEPSS Scores of Improvement Group and Non-improvement Group After 12 Weeks of Clozapine Treatment

	Improvement Group	Non-improvement Group	*P*
Gait	0.17 ± 0.41	1.00 ± 0.82	0.062
Bradykinesia	0.33 ± 0.52	2.00 ± 0.82	0.0039
Sialorrhea	0.50 ± 0.84	2.00 ± 0.82	0.024
Rigidity	0.00 ± 0.00	0.75 ± 0.96	0.083
Tremor	0.00 ± 0.00	2.00 ± 0.82	0.0003
Akathisia	0.00 ± 0.00	1.00 ± 1.16	0.06
Dystonia	0.00 ± 0.00	0.00 ± 0.00	
Dyskinesia	0.00 ± 0.00	0.00 ± 0.00	
Overall severity	0.67 ± 0.82	2.25 ± 0.50	0.0089



There was a significant interaction between DIEPSS overall severity and improvement in CGI-I (F = 8.26, *p*= 0.021).

Figure 1. Overall Severity of DIEPSS Scores in Improvement Group and Non-improvement Group Just Before and After 12 Weeks of Clozapine (CL) Treatment



There was a significant tendency of interaction between biperiden equivalent doses and improvement in CGI-I ($F = 4.68$, $p = 0.063$).

Figure 2. Relationship Between Biperiden Equivalent Dose and Improvement in CGI-I Just Before and After 12 Weeks of Clozapine (CL) Treatment

DISCUSSION

In the present study, clozapine responders experienced significantly fewer extrapyramidal symptoms from switching to after 12 weeks of clozapine treatment than clozapine non-responders. Moreover, clozapine responders had a significant tendency to reduce their use of antiparkinson drugs from switching to after 12 weeks of clozapine than clozapine non-responders. These findings suggest that clozapine responders are likely to suffer from fewer extrapyramidal symptoms. In contrast to the findings of Umbricht et al. [5] where clozapine responders exhibited fewer extrapyramidal symptoms at baseline than non-responders, clozapine responders had comparable extrapyramidal symptoms at baseline (just before clozapine treatment) as non-responders in the present study.

It is unknown why clozapine responders may have fewer extrapyramidal symptoms than non-responders. However, several PET studies revealed that clozapine may bind preferentially to extra-striatal dopamine receptors than striatal dopamine receptors (D_1 receptors were investigated by Chou et al. [6]; D_2 receptors by Kessler et al. [7]; and D_2/D_3 receptors by Gründer et al. [8]), although Talvik et al. [9] did not find such regional selectivity in clozapine-treated patients. If clozapine truly binds preferentially to extra-striatal dopamine receptors, clozapine-treated patients may suffer from fewer extrapyramidal symptoms because striatal dopamine D_2 receptors' occupancy correlated positively to extrapyramidal symptoms [10]. Although these findings can partially account for why clozapine responders may experience fewer extrapyramidal symptoms, it is still unknown why clozapine non-responders may experience more extrapyramidal symptoms.

Blockade of dopamine D_2 receptors remains a common feature of all antipsychotics. Although it has been hypothesized that the extra-striatal dopamine D_2 receptors may be more critical to antipsychotic response than the striatal dopamine D_2 receptors, Agid et al. [11] investigated risperidone and olanzapine and reported that striatal D_2 occupancy predicted response in positive psychotic symptoms, but not in negative symptoms, whereas extrastriatal D_2 occupancy did not predict response in positive or negative symptoms, suggesting that dopamine D_2 blockade within specific regions of the striatum may be the most critical factor for ameliorating psychosis in schizophrenia. Also, Kegeles et al. [12] investigated aripiprazole and showed that positive (but not negative) symptom improvement correlated with striatal but not extrastriatal occupancies, again suggesting the importance of dopamine D_2 modulation of striatal rather than cortical or other extrastriatal dopaminergic neurons. These recent findings indicate that antipsychotic effects may be mainly related to striatal D_2 occupancy. However, if this is the case, our clozapine non-responders should have become responders because their higher incidence of extrapyramidal symptoms suggested that their striatal D_2 occupancy might have been higher than that of clozapine responders. In addition, the aforementioned assumption that clozapine may bind preferentially to extra-striatal dopamine receptors than striatal dopamine receptors may be inconsistent with the

assumption that antipsychotic effect is mainly related to striatal D_2 occupancy.

Vanquelin et al. [13] performed simulations and showed that the low propensity of clozapine to elicit extrapyramidal symptoms is related to a rather unique combination of its pharmacodynamic (i.e., the ability to allow increased D_2 receptor stimulation by endogenous dopamine during high activity periods) and pharmacokinetic (i.e., fast fluctuating D_2 receptor occupancy between successive doses) properties, but that this combination precludes the traditional "beneficial" 60% receptor occupancy threshold from being continuously exceeded at every hour of every day. Therefore, this model cannot fully account for clozapine's effects and it is still unknown whether clozapine's effects are mainly related to striatal D_2 occupancy.

Interestingly, as shown in Figure 1, there was a significant interaction between DIEPSS overall severity and improvement in CGI-I. Moreover, as shown in Figure 2, there was also a significant tendency of interaction between biperiden equivalent doses and improvement in CGI-I. It appears that a non-dopaminergic action (e.g., serotonin, NMDA) may also contribute to clozapine's effects [14]. Further studies are required to clarify why clozapine responders may experience fewer extrapyramidal side effects.

However, it should be noted that the relationship between extrapyramidal liability and poor response is not specific to clozapine. It has been known for a long time that a propensity for extrapyramidal side effects is related to nonresponse [15] and tardive dyskinesia [16], which is also related to a poor prognosis, suggesting that a relationship between extrapyramidal liability and poor response is common in antipsychotic use. The present findings therefore suggest that clozapine is not exceptional in this regard. Nonetheless, the new finding of the present study is that clozapine responders are likely to experience fewer extrapyramidal symptoms during clozapine treatment, suggesting that they can continue to receive clozapine until they suffer from other severe side effects.

The limitations of the present study were the small sample size, the absence of plasma clozapine concentration data, and that the patients had been treated with other antipsychotics.

In conclusion, although the present findings suggest that clozapine responders are likely to experience fewer extrapyramidal symptoms, given the above limitations, further studies are required to substantiate these findings.

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