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Case Report

Efficacy and tolerability of blonanserin in 48 patients with intractable schizophrenia

Takaki M, Okahisa Y, Kodama M, Mizuki Y, Sakamoto S, Ujike H, Uchitomi Y. Efficacy and tolerability of blonanserin in 48 patients with intractable schizophrenia.

Background: Blonanserin is effective for the treatment of schizophrenia in Korea and Japan.
Methods: We administered blonanserin to 48 Japanese patients with schizophrenia for whom other atypical antipsychotics were not sufficiently effective or tolerated.
Results: Previous antipsychotics were replaced with blonanserin because of its effectiveness (54.2%; 26/48) or tolerability (45.8%; 22/48). Blonanserin was more effective in 65.4% (17/26) of the and better tolerated in 95.5% (21/22) of the patients. Of 48 patients, 33 continued blonanserin for 1 year. The mean Clinical Global Impression of Severity scores improved from 4.60 to 2.48. The mean Global Assessment of Functioning score improved from 29.8 to 51.7. Nineteen patients (39.6%; 19/48) had a social role. The reasons for discontinuation of blonanserin were ineffectiveness against psychosis (27.1%; 13/48) or intolerability (4.2%; 2/48). The ratio of discontinuation for intolerability versus ineffectiveness was 0.15, which was the lowest among atypical psychotics.
Conclusions: Blonanserin may be effective and safe for the treatment of intractable schizophrenia.

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Keywords: blonanserin; effectiveness; intractable schizophrenia; social function; tolerability

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Introduction

Atypical antipsychotics are characterised by a potent serotonin (5-HT)-2 receptor-blocking action in addition to D2 antagonism. Atypical antipsychotics have the same efficacy as typical antipsychotics but a lower risk of extrapyramidal symptoms (EPS) and impaired cognition (1). However, they have potentially serious side effects, including weight gain, sedation, akathisia and hyperprolactinaemia (1). Therefore, new atypical antipsychotics with a better safety profile suitable for long-term management of patients with schizophrenia have long been sought.

Blonanserin (2-(4-ethyl-l- piperazinyl)-4-(4-fluorophenyl)-5,6,7,8,9,10-hexahydrocycloocta [b]pyridine) has a D2 receptor-blocking activity comparable to that of haloperidol, as well as potent 5-HT-2 receptor-blocking activity and weak 5TH-2C, D1 and α_1 receptor-blocking activities while being almost devoid of histamine H1 and muscarinic M1 antagonist activity (2,3). Blonanserin displays a positive atypical index equal to that of sulpiride (4).

Clinical trials have shown that blonanserin is effective in the treatment of both positive and negative symptoms of schizophrenia in Japan and Korea (5–7). In a Japanese study, blonanserin improved memory 1 and 2 scores on the Wechsler memory scale-revised (WMS-R) and attention scores on the Wechsler adult intelligence scale-revised (WAIS-R) (8). In this study, we administered blonanserin to 48 Japanese patients with schizophrenia for whom other atypical antipsychotics were not sufficiently effective or tolerated. The objective was to evaluate the effectiveness and tolerability of blonanserin and its ability to induce social functions in the treatment of Japanese patients with intractable schizophrenia.

Cases and methods

Blonanserin was administered to 48 patients [14 male and 34 female, aged 21–68 years, mean 42.31 years (±12.24)] with 45 schizophrenia and 3

schizoaffective disorder as diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-4). The diagnosis was performed with the clinical features by the attending psychiatrist and the other two investigators. The subtypes of schizophrenia were 34 paranoid, 10 hebephrenic and 1 catatonic. Fourteen patients had the hereditary form of schizophrenia. Other atypical antipsychotics were not effective or well tolerated. The average duration of illness was 16.81 years. Thirty-seven patients had a history of hospitalisation, and 25 patients were in-patients before the switch to blonanserin. According to the clozapine treatment and monitoring guidelines in Japan, 24 patients had treatment-resistant schizophrenia and 9 patients had treatment-intolerant schizophrenia (9). Clozapine had not been administered to these patients because clozapine was not available in Japan until April 2010. Fifteen psychiatrists diagnosed and participated in their treatment. This is a retrospective study based on medical records by psychiatrists who were not the attending psychiatrists. The Clinical Global Impression of Severity (CGI-S) score, Global Assessment of Functioning (GAF) score and social role of the patients were assessed before the switch to blonanserin and at the cutoff point or 1 year after switching to blonanserin. No other antipsychotic was administered at the same time as blonanserin. We investigated the reasons for the discontinuation of previous antipsychotics and initiation of blonanserin, the efficacy of blonanserin and the improvement in social function 1 year after blonanserin therapy.

Results

They had been administered an average of 1.98 (±1.08) classes of atypical antipsychotics. An adjunct anticholinergic, biperiden, was administered to 12 patients (25%) at an average dose of 2.08 mg/day. An adjunctive mood stabiliser was given to 15 patients (31.3%): valproic acid to 12, lithium to 2 and carbamazepine to 1. Before switching to blonanserin, the 48 Japanese intractable schizophrenia patients were treated with risperidone (13), olanzapine (13), aripiprazole (11), quetiapine (5), perospirone (2) and typical antipsychotics (4). They were switched to blonanserin for its effectiveness (54.2%; 26/48) or tolerability (45.8%; 22/48). The average maximum dose of blonanserin was 13.89 mg/day (±18.5). Blonanserin improved the effectiveness of 65.4% (17/26) of cases and the tolerability in 95.5% (21/22) of cases. Twenty-two cases were switched to blonanserin because of intolerance to other antipsychotics, including six cases of sedation, six cases of amenorrhoea, three cases of akathisia, two cases of dystonia, two cases of extrapyramidal signs, one cases of high serum creatine phosphokinase, one case of obesity and one case of headache. The six cases of amenorrhoea included three cases of hyperprolactinaemia. One patient who switched because of sedation still felt sedated after switching to blonanserin and dropped out. Of 48 patients, 33 patients continued blonanserin for 1 year. The mean CGI-S scores improved from 4.60 (±1.31) to 3.19 (±1.58). The CGI-S scores of the 33 patients who continued blonanserin for 1 year were improved to 2.48 (±1.12). The mean GAF score improved from 29.8 (±10.9) to 51.7 (±16.8). The maintenance dose of blonanserin was 11.52 mg/day (±7.94). Twenty-two cases were maintained at the maximum dose, and it was decreased in 11 cases. Among the 33 patients who continued blonanserin, 19 patients (39.6%; 19/48) were able to function socially, 11 as full-time housewives, 4 as full-time workers and 4 as part-time workers. Before blonanserin administration, only the patient having akathisia was able to work, and the other 18 were not able to function socially. Blonanserin was discontinued because it was ineffective against psychosis (27.1%; 13/48) or not well tolerated (4.2%; 2/48). Blonanserin was also discontinued because it caused akathisia and sedation. The ratio of discontinuation for intolerance versus ineffectiveness was 0.15, which was the lowest among all atypical psychotics (Table 1).

Discussion

The ratio of discontinuation for intolerance versus effectiveness of blonanserin was the lowest among the atypical psychotics (Table 1). On the other hand, the discontinuation ratios of risperidone and olanzapine were high (Table 1). In this study, blonanserin was effective in 65% of Japanese patients with intractable schizophrenia. Other open label studies have indicated that blonanserin was as effective as risperidone or haloperidol (5–7). In addition, blonanserin was well tolerated and had a better safety profile. Risperidone induced amenorrhoea, hyperprolactinaemia, EPS and dystonia. These adverse events were related to D2 receptor-blocking activity (1). Blonanserin blocked D2 receptor activity more strongly than risperidone or haloperidol,but blonanserin induced these side effects at a lower rate in our study. Blonanserin more strongly blocks 5HT2A activity than risperidone (2) and therefore might induce lower rates of EPS and dystonia. Recently, atypical psychotics were reported to have different risks of hyperprolactinaemia, and this is related to the drug concentrations in the brain and plasma (10). Blonanserin crosses the blood–brain barrier at higher levels than risperidone

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Table 1. Reason for discontinuation of atypical psychotics in 48 Japanese patients with intractable schizophrenia

	Maximum dose (mg) (±SD)	Discontinuation		
		Ratio	Ineffective	Intolerance
Blonanserin	13.89 (±18.50)	0.15	13	2
Quetiapine	511.36 (±264.42)	0.35	8	3
Aripiplazole	15.43 (±8.29)	0.4	15	6
Perospirone	23.27 (±14.06)	0.83	6	5
Risperidone	4.44 (±2.44)	1.82	11	20
Olanzapine	11.60 (±5.67)	2.5	6	15

	Intolerance							
	EPS	Dystonia	Akathisia	Amenorrhoea	Sedation	Obesity	Headache	CPK
Blonanserin	0	0	1	0	1	0	0	0
Quetiapine	0	0	0	0	1	1	0	1
Aripiplazole	0	0	4	0	0	0	1	1
Perospirone	0	0	0	0	4	0	0	1
Risperidone	3	3	1	7	4	1	0	1
Olanzapine	1	1	0	1	7	5	0	0

CPK, elevated creatine phosphokinase; EPS, extrapyramidal symptoms. Ratio: ratio of discontinuation for intolerance versus ineffectiveness.

or haloperidol (10). Blonanserin was reported to induce akathisia more frequently than risperidone or haloperidol (5–7). In our study, blonanserin induced five cases of akathisia, but four patients continued blonanserin after the dose was reduced or biperiden was added. Five patients who had reported akathisia while taking aripiprazole or risperidone were able to continue blonanserin. For management of akathisia, the dose of blonanserin might be important. Blonanserin improved obesity and sedation. Blonanserin has weak 5TH2C and α_1 receptor-blocking activities while being almost devoid of histamine H1 activity (2,3). In our study, 57.6% of the patients who continued blonanserin functioned socially. Blonanserin has D3 receptor-binding affinity (2). Because a selective blockade of D3 receptors enhances frontocortical cholinergic transmission, D3-receptor function is related to social recognition in humans and rodents (11,12).

There are some limitations in this study. The diagnosis was performed considering clinical features alone. Three patients with schizoaffective disorder were included. It was difficult to evaluate CGI-S, GAF and social functioning retrospectively. Therefore, the validity and bias might be included.

Fifteen percent of the patients with chronic schizophrenia were reported to discontinue risperidone (RIS), olanzapine (OLZ) or quetiapine (QTP) owing to intolerance within 18 months (1). The intolerance of the antipsychotics is one of the important factors to continue the treatment of schizophrenia. Blonanserin may be suitable for the long-term management of patients with intractable schizophrenia.

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References

1. Lieberman JA, Stroup TS, Mcevoy JP et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. N Engl J Med 2005;**353**:1209–1223.
2. Deeks ED, Keating GM. Blonanserin: a review of its use in the management of schizophrenia. CNS Drugs 2010;**24**:65–84.
3. Noda Y, Kurumiy S, Miura Y, Oka M. Comparative study of 2-(4-ethyl-1-piperazinyl)-4-(fluorophenyl)-5,6,7,8,9, 10-hexahydrocycloocta[b]pyridine (AD-5423) and haloperidol for their pharmacological activities related to antipsychotic efficacy and/or adverse side-effects. J Pharmacol Exp Ther 1993;**265**:745–751.
4. Oka T, Hamamura T, Lee Y et al. Atypical properties of several classes of antipsychotic drugs on the basis of differential induction of Fos-like immunoreactivity in the rat brain. Life Sci 2004;**76**:225–237.
5. Murasaki M. Clinical evaluation of blonanserine for schizophrenia: double-blind comparing blonanserin with haloperidol. Jpn J Clin Psychopharmacol 2007;**10**:2059–2079.
6. Garcia E, Robert M, Peris F, Nakamura H, Sato N, Terazawa Y. The efficacy and safety of blonanserin compared with haloperidol in acute-phase schizophrenia: a randomized, double-blind, placebo-controlled, multicentre study. CNS Drugs 2009;**23**:615–625.
7. Yang J, Bahk WM, Cho HS et al. Efficacy and tolerability of blonanserin in the patients with schizophrenia: a randomized, double-blind, risperidone-compared trial. Clin Neuropharmacol 2010;**33**:169–175.
8. Miura S. Effect of new-generation antipsychotics blonanserin on cognitive impairment in schizophrenia. Jpn J Clin Psychopharmacol 2008;**11**:315–326.

https://doi.org/10.1111/j.1601-5215.2012.00663.x Published online by Cambridge University Press

9. Oshimo T. Clozapine treatment and monitoring guideline in Japan. Jpn J Clin Psychopharmacol 2009;**59**:1375–1384.
10. Arakawa R, Okumura M, Ito H et al. Positron emission tomography measurement of dopamine D2 receptor occupancy in the pituitary and cerebral cortex: relation to antipsychotic-induced hyperprolactinemia. J Clin Psychiatry 2010;**71**:1131–1137.
11. Millan MJ, Di Cara B, Dekeyne A et al. Selective blockade of dopamine D(3) versus D(2) receptors enhances frontocortical cholinergic transmission and social memory in rats: a parallel neurochemical and behavioural analysis. J Neurochem 2007;**100**:1047–1061.
12. Bombin I, Arango C, Mayoral M et al. DRD3, but not COMT or DRD2, genotype affects executive functions in healthy and first-episode psychosis adolescents. Am J Med Genet B Neuropsychiatr Genet 2008;**147B**:873–879.

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