

A naturalistic comparison of the efficacy and safety of intramuscular olanzapine and intramuscular levomepromazine in agitated elderly patients with schizophrenia

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Background: There have not been any reports in Japan clarifying the efficacy and safety of intramuscular (IM) olanzapine and IM levomepromazine in agitated elderly patients with schizophrenia. This study was a comparative investigation of the clinical efficacy and safety of IM olanzapine and IM levomepromazine in agitated elderly patients with schizophrenia at 2 hours post-dose.

Methods: The subjects were 52 inpatients who were diagnosed with schizophrenia according to the *Diagnostic and Statistical Manual of Mental Disorders* (DSM)-IV. Their clinical symptoms were assessed using the Positive and Negative Syndrome Scale Excited Component (PANSS-EC), PANSS, and Agitation Calmness Evaluation Scale (ACES), and their safety was assessed using the Abnormal Involuntary Movement Scale (AIMS), Barnes Akathisia Rating Scale (BARS), Drug-Induced Extrapyramidal Symptoms Scale (DIEPSS), and glucose test.

Results: The PANSS-EC total score, the ACES score, and the glucose level significantly decreased from baseline in both the IM olanzapine group and the levomepromazine injection group; however, no between-group differences were observed. Mean change from baseline in the PANSS total score, positive score, the BARS score, and the DIEPSS total score was significantly greater in the IM olanzapine injection group compared with the levomepromazine injection group.

Conclusion: The results of this study suggest that agitated elderly patients rapidly respond to IM olanzapine and IM levomepromazine treatment. Furthermore, these results suggest that IM olanzapine is safer than IM levomepromazine and causes greater improvement in positive symptoms.

Keywords: intramuscular olanzapine, intramuscular levomepromazine, acute agitation, elderly schizophrenia, positive symptoms, safety

Introduction

In the acute stage of schizophrenia, patients are often in an agitated state (eg, irritable, excited) and may exhibit animosity. During this phase, worsening of positive and catatonic symptoms as well as emotional changes can occur. The most important treatment for these acute symptoms is to promptly control the aggression and acute agitation exhibited frequently by the patients.¹⁻³

Elderly patients generally have reduced liver/kidney function and increased susceptibility to adverse drug reactions. Furthermore, because of adverse drug reactions, elderly patients are more likely to experience a reduction in activities of daily living and in their quality of life. Due to a decreased capacity for reality testing combined

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with a lack of insight, such elderly patients are more likely to miss their medication or make mistakes while taking their medication, leading to severely inadequate treatment adherence. Consequently, psychiatric symptoms can occasionally become unstable and acute-stage symptoms can emerge. Therefore, when determining the drug therapy for elderly patients with schizophrenia, it is important to choose a drug that can be taken reliably and has a better adverse-reaction profile. In addition, the treatment should be initiated soon after the onset of acute-stage symptoms so that no higher dose is used than what is necessary.

Until now, injectable formulations of atypical antipsychotics have not been used in a clinical setting in Japan; intramuscular (IM) or intravenous formulations of typical antipsychotics and/or benzodiazepines are normally opted for instead.⁴⁻⁶ Haloperidol or levomepromazine are the injectable, atypical antipsychotics. The latter is not marketed in the United States; however, diazepam is often used as an injectable benzodiazepine formulation. For haloperidol and levomepromazine, there are some differences between the pharmacokinetics of the IM formulations and oral formulations, and the onset of effects in IM formulations is more rapid.⁷⁻⁹ However, injectable formulations of typical antipsychotics are clinically problematic because they can cause akathisia, acute dystonia, neuroleptic malignant syndrome, and electrocardiogram abnormalities such as QTc interval prolongation.¹⁰⁻¹⁵ Moreover, injectable formulations of benzodiazepines can result in respiratory depression and, thus, are also clinically unsuitable.^{16,17}

Therefore, IM olanzapine has been approved in more than 70 countries worldwide for early-stage treatment of schizophrenia and is now one of the first chosen drugs in parenteral drug therapy.^{18,19} IM olanzapine has the same pharmacokinetics as oral olanzapine; however, the time of onset is shorter since it is rapidly absorbed following IM administration.²⁰

IM olanzapine has been available in Japan since December 2012; however, there are no reports regarding its use in agitated, elderly Japanese patients with schizophrenia. Thus, in this study, we investigated the clinical efficacy and safety of IM olanzapine and IM levomepromazine in agitated, elderly Japanese patients with schizophrenia.

Methods

Subjects

Fifty-two inpatients undergoing treatment at the psychiatry departments of Tanzawa Hospital or Seimo Hospital were enrolled in this study; they all were diagnosed with

schizophrenia according to the *Diagnostic and Statistical Manual of Mental Disorders* (DSM)-IV. All participants were elderly patients with schizophrenia (age >60 years) with persisting symptoms and undergoing antipsychotic monotherapy. The inclusion criteria were as follows: all patients (1) had a total score of 14 or higher on the Positive and Negative Syndrome Scale Excited Component (PANSS-EC) with a score of 4 or higher on at least one item, and the treating psychiatrist concluded that the patient needed to be treated with an IM injection; (2) were able to provide informed consent or cooperate with the requirements of the study; and (3) were treated previously with a stable dose of an oral antipsychotic drug monotherapy for at least 3 months. The exclusion criteria were as follows: (1) exhibition of allergic reactions or resistance to olanzapine or levomepromazine; (2) any clinically significant organic or neurological disease; and (3) any serious internal medical comorbidity. In other words, patients with hyperglycemia (casual blood glucose ≥ 200 mg/dL or HbA_{1c} $\geq 5.9\%$), dehydration, physical exhaustion accompanied by poor nutritional status, liver disorder, or cardiovascular disorder were excluded from the study. Patients meeting the following concomitant therapy criteria were also excluded to elucidate the differences between the efficacy of IM olanzapine and IM levomepromazine: patients receiving oral olanzapine or levomepromazine and patients receiving benzodiazepine receptor agonists within 4 hours prior to IM administration. The IM olanzapine injection group and the IM levomepromazine injection group were recruited separately. There were no other medications besides the studied antipsychotic drugs.

The study was an open-labeled, flexible-dose, naturalistic observational trial of schizophrenia patients who required an additional medication for acute agitation. There was no difference in the observed side effects and symptoms between the IM olanzapine injection group and the IM levomepromazine injection group. Given that olanzapine injection was not introduced into a clinical setting until November 2012, all patients first received IM levomepromazine injections (25 mg). From December 2012 to March 2013, most patients received IM olanzapine injection (5.0, 7.5, or 10.0 mg); however, some patients continued to receive IM levomepromazine injections because IM olanzapine injections could not be used by the admitting department due to its cost.

This study was conducted in accordance with the Declaration of Helsinki and all necessary official approvals were obtained to conduct examinations at each hospital site.

Because this study was conducted on patients who experienced worsening symptoms while in hospital and presented with psychomotor excitability, the study goal was explained to them. Advanced written consent was obtained from each participant when in a mental state deemed capable of giving permission.

Assessment methods

Clinical assessments were performed both at baseline and at 2 hours after IM administration by the psychiatrist who provided the therapy. Therefore, the evaluator was not blind to the patient's treatment. There were no reliability tests for those who utilized the PANSS-EC (tension, uncooperativeness, hostility, poor impulse control, and excitement),²¹ PANSS,²² Agitation Calmness Evaluation Scale (ACES), a single-item, 9-point scale (1 = marked agitation; 2 = moderate agitation; 3 = mild agitation; 4 = normal behavior; 5 = mild calmness; 6 = moderate calmness; 7 = marked calmness; 8 = deep sleep; 9 = unarousable), Abnormal Involuntary Movement Scale (AIMS),²³ Barnes Akathisia Rating Scale (BARS),²⁴ and the Drug-Induced Extrapyramidal Symptoms Scale (DIEPSS), 9-item (gait, bradykinesia, sialorrhea, muscle rigidity, tremor, akathisia, dystonia, dyskinesia, and overall severity), 5-point scale (0 = normal; 1 = minimal; 2 = mild; 3 = moderate; 4 = severe).^{25,26} However, assessor training was provided to ensure a certain degree of reliability. Changes in the PANSS-EC score, PANSS score, and ACES score were chosen as efficacy outcomes. Because the PANSS-EC score (1) has high face validity in the measurement agitation; (2) is rated by physician observations as opposed to patient participation and thus is well suited for the assessment

of agitation because it avoids the need for interaction that could exacerbate agitation. Agitation was further assessed with ACES. The PANSS score was used to assess general psychiatric status.

Meanwhile, the AIMS, BARS, DIEPSS, vital sign (pulse and blood pressure), and blood glucose level tests were used to investigate safety. The AIMS, BARS, and DIEPSS were used to assess extrapyramidal symptoms.

Statistical analysis

The following statistical methods were used.

- For comparison of baseline demographics: Fisher's exact tests and analysis of variance (ANOVA).
- For change in symptoms over time (within groups): paired *t*-tests. If the data did not show a normal distribution, then the Wilcoxon signed rank sum test was used instead.
- For change in symptoms over time (between groups): repeated measures ANOVA, group/time interaction (at baseline and 2 hours after IM administration). The categorical variable was between groups, and the compact variable was time interaction of each rating scale.

The significance level was $P < 0.05$ in all analyses.

Results

Subject profiles (Table 1)

There were no significant differences between the IM olanzapine injection group and the IM levomepromazine injection group regarding baseline PANSS-EC total score, baseline PANSS total score, baseline ACES score, baseline BARS total score, baseline DIEPSS total score, mean daily dosage of the previous treatment drug, mean duration of illness, and

Table 1 Subject characteristics

Characteristics	IM olanzapine group (n = 27)	IM levomepromazine group (n = 25)	P-value
Age (years) (mean ± SD)	64.2 ± 4.0	64.5 ± 2.6	0.89
Sex (M:F), n (%)	15 (55.6):12 (44.4)	9 (36):16 (64)	0.10
Duration of illness (years) (mean ± SD)	40.9 ± 7.2	40.4 ± 7.3	0.82
Chlorpromazine equivalents dose (mg/day) (baseline) (mean ± SD)	533.3 ± 172.4	494.0 ± 257.0	0.52
Biperiden equivalents dose (mg/day) (baseline) (mean ± SD)	0.9 ± 1.2	0.6 ± 1.0	0.29
Diazepam equivalents dose (mg/day) (baseline) (mean ± SD)	6.9 ± 6.7	9.8 ± 11.6	0.27
Sodium valproate dose (mg/day) (baseline) (mean ± SD)	81.5 ± 168.8	64.0 ± 149.7	0.70
ACES score (baseline) (mean ± SD)	2.6 ± 0.7	2.4 ± 0.7	0.35
PANSS total score (baseline) (mean ± SD)	97.9 ± 10.8	103.5 ± 16.2	0.15
PANSS-EC score (baseline) (mean ± SD)	17.6 ± 2.4	18.3 ± 2.2	0.24
AIMS total score (baseline) (mean ± SD)	6.2 ± 3.8	9.6 ± 3.1	0.0008
BARS total score (baseline) (mean ± SD)	1.2 ± 1.8	0.5 ± 1.1	0.09
DIEPSS total score (baseline) (mean ± SD)	7.2 ± 3.1	7.2 ± 2.7	0.94

Abbreviations: IM, intramuscular; SD, standard deviation; ACES, Agitation Calmness Evaluation Scale; PANSS, Positive and Negative Syndrome Scale; PANSS-EC, Positive and Negative Syndrome Scale Excited Component; AIMS, Abnormal Involuntary Movement Scale; BARS, Barnes Akathisia Rating Scale; DIEPSS, Drug-Induced Extrapyramidal Symptoms Scale.

mean age. However, there was a significant difference in the baseline AIMS total score.

According to DSM-IV criteria, 15 patients (55.6%) showed paranoia, nine patients (33.3%) were disorganized, and three patients (11.1%) were residual in the IM olanzapine injection group; while 16 patients (64.0%) showed paranoia, seven patients (28.0%) were disorganized, and two patients (8.0%) were residual in the IM levomepromazine injection group.

The mean duration of antipsychotic medication before the IM trial started was 16.3 ± 3.1 months for the IM olanzapine injection group and 16.5 ± 3.6 months for the IM levomepromazine injection group.

Both groups in this study received the following antipsychotics: in the IM olanzapine injection group, 22.2% (6/27) received paliperidone, 11.1% (3/27) received risperidone, and 66.7% (18/27) received risperidone long-acting injection; while in the IM levomepromazine injection group 32.0% (8/25) received paliperidone, 20.0% (5/25) received risperidone, and 48.0% (12/25) received risperidone long-acting injection. The only concomitant mood stabilizer used in this study was sodium valproate, which was used by 22.2% (6/27) of the IM olanzapine injection group and 16.0% (4/25) of the IM levomepromazine injection group.

The average medication dose of both groups was 6.9 ± 2.4 mg for the IM olanzapine injection group and 25 mg for the IM levomepromazine injection group.

Efficacy (Table 2)

The PANSS-EC total score and the ACES score significantly decreased from baseline in both the IM olanzapine and the IM levomepromazine injection group; however, no between-group differences were observed. Mean reduction from baseline in the PANSS total score and positive score was significantly greater in the IM olanzapine injection group compared with the IM levomepromazine injection group. The delusion and suspiciousness in positive symptoms were improved mainly in the IM olanzapine injection group compared with the IM levomepromazine injection group.

Safety (Table 2)

Regarding the BARS score and the DIEPSS total score, mean change from baseline was significantly better in the IM olanzapine injection group than in the IM levomepromazine injection group. Regarding systolic and diastolic blood pressure, mean change from baseline was miniscule in both the groups. Glucose level (mg/dL) significantly decreased

Table 2 Efficacy and safety

	IM olanzapine group (n = 27)				IM levomepromazine group (n = 25)				F-value ^a	P-value
	Baseline		Change from baseline to after 2 hours		Baseline		Change from baseline to after 2 hours			
	Mean	SD	Mean	SD	Mean	SD	Mean	SD		
ACES	2.6	0.7	1.4	0.8 ^b	2.4	0.7	1.5	0.6 ^b	0.33	0.57
PANSS										
Total	97.9	10.8	-8.5	2.9 ^b	103.5	16.2	-6.9	2.1 ^b	5.38	0.025
Positive	23.7	3.2	-4.6	1.8 ^b	25.2	2.7	-3.5	1.0 ^b	8.14	0.006
Negative	27.0	4.9	-	-	28.3	7.0	-	-	-	-
General psychopathology	47.1	4.8	-5.3	5.6 ^b	49.7	8.8	-3.4	1.2 ^b	2.60	0.11
PANSS-EC	17.6	2.4	-6.4	2.1 ^b	18.3	2.2	-6.4	1.8 ^b	-	0.99
AIMS total score	6.2	3.8	-0.2	0.8	9.6	3.1	0.0	0.0	1.92	0.17
BARS total score	1.2	1.8	-0.8	1.5 ^c	0.5	1.1	-0.3	0.7	2.24	0.14
DIEPSS total score	7.2	3.1	-0.3	0.6 ^c	7.2	2.7	0.0	0.0	7.21	0.01
Pulse rate	75.4	12.0	1.1	12.0	71.1	13.0	3.6	9.4	0.64	0.43
Systolic blood pressure (mmHg)	121.9	11.7	2.7	10.3	124.1	16.7	-2.0	17.8	1.29	0.26
Diastolic blood pressure (mmHg)	77.8	12.9	-1.8	10.3	72.3	10.2	3.3	0.7	4.05	0.50
Glucose (mg/dL)	115.9	33.8	-6.5	14.1 ^b	100.0	15.7	-4.4	12.2 ^b	0.29	0.59

Notes: ^aF-value: repeated measures ANOVA – the groups (IM olanzapine group and IM levomepromazine group) × time interaction (at baseline and 2 hours after IM administration) of each rating scale; ^bP < 0.005 versus baseline; ^cP < 0.05 versus baseline.

Abbreviations: IM, intramuscular; SD, standard deviation; ACES, Agitation Calmness Evaluation Scale; PANSS, Positive and Negative Syndrome Scale; PANSS-EC, Positive and Negative Syndrome Scale Excited Component; AIMS, Abnormal Involuntary Movement Scale; BARS, Barnes Akathisia Rating Scale; DIEPSS, Drug-Induced Extrapyramidal Symptoms Scale; ANOVA, analysis of variance.

from baseline in both the groups; however, there was no between-group differences.

Adverse events (Table 3)

The incidence of adverse events at the injection site, which is mild pain, was 3.7% (1/27) in the IM olanzapine injection group and 8.0% (2/25) in the IM levomepromazine injection group. No redness, swelling, or induration was observed. The most common adverse events in the IM olanzapine injection group were increased blood pressure, somnolence, dizziness, and thirst. The most common adverse events in the IM levomepromazine injection group were increased blood pressure, low blood pressure (systolic blood pressure <100 mmHg), somnolence, and dizziness. Most adverse events were rated mild, and no serious adverse events, such as paralytic ileus, diabetic ketoacidosis, neuroleptic malignant syndrome, or tardive dyskinesia were noted.

Discussion

According to the most recent expert consensus guidelines for the use of antipsychotic drugs for agitation with psychosis, IM olanzapine, and IM ziprasidone are the first drugs of choice among available non-oral therapies, and IM haloperidol with benzodiazepine is the second-line therapy.²⁷ In this study, we compared the efficacy and safety of IM olanzapine and IM levomepromazine, two most frequently used non-oral therapies in routine clinical practice in Japan, 1 hour post-administration.

Levomepromazine is a phenothiazine first-generation antipsychotic drug that has a weak dopamine (D_2) receptor blocking effect and a strong 5-HT_{2A} receptor blocking effect. It is also a powerful blocker of α_1 receptor and H₁ receptor as well as a powerful sedative. On the basis of its pharmacological profile, the results of this study suggest that IM levomepromazine and IM olanzapine have similar capacity to improve poor impulse and excitement.

In contrast, because olanzapine has a stronger affinity for dopamine (D_2) receptors than levomepromazine,

a significantly better improvement in positive symptoms was observed with IM olanzapine than with IM levomepromazine. These results are consistent with those of our previous research and other studies.^{28,29}

Our results suggest that IM olanzapine, but not IM levomepromazine, prevents the emergence of drug-induced extrapyramidal symptoms; generally, this is one of the risk factors for reduced activities of daily living in elderly patients. These findings are consistent with those of previous studies.^{30–32} However, the mean score of the AIMS at baseline for the two groups differed significantly, which is a limitation of these findings.

In elderly patients, arrhythmias result in symptoms, such as dizziness, palpitations, and shortness of breath, which are contributing factors for a poor prognosis. The results of this study demonstrate that both IM olanzapine and IM levomepromazine did not affect pulse rate. Hypertension is a risk factor for cardiovascular disease. Furthermore, in elderly patients, hypotension is accompanied by lightheadedness and therefore increases the risk of falls and bone fractures. Although the results of this study highlight that IM olanzapine results in increased blood pressure, it remained within the normal range for all subjects. In contrast, IM levomepromazine resulted in decreased blood pressure in 24% of our patients. Therefore, the results of this study show that IM levomepromazine affects blood pressure. In a large-scale study conducted in Norway, the risk of death was found to be lower after levomepromazine administration compared with after haloperidol administration.³³ However, in a study conducted in Japan, levomepromazine resulted in significant QTc prolongation.³⁴ Levomepromazine also possesses a powerful α_1 receptor blocking effect and an anticholinergic effect. Therefore, caution must be exercised regarding the possible emergence of, among other events, lightheadedness, falls, over-sedation, low blood pressure, and delirium, particularly if it is going to be used in the elderly patients. Both the results of this study and those of previous studies suggest that IM olanzapine may be safer than IM levomepromazine. However, treatment with olanzapine could result in fatal outcomes due to diabetic ketoacidosis, diabetic coma, for example, because of a marked increase in glucose level. To be safe, we monitored changes in glucose levels 2 hours after the administration of IM olanzapine. Consistent with the results of previous research, we found that glucose levels were higher in the IM levomepromazine than in IM olanzapine group, and our findings suggest that IM olanzapine may have little adverse effect on glucose levels. In order to elucidate the differences in the efficacy and safety among

Table 3 Adverse events

	Number (%) of patients	
	IM olanzapine group (n = 27)	IM levomepromazine group (n = 25)
Blood pressure increased	3 (11.1)	1 (4.0)
Low blood pressure	0	6 (24.0)
Somnolence	3 (11.1)	3 (12.0)
Suspensibility dizziness	2 (7.4)	3 (12.0)
Thirst	1 (3.7)	0

Abbreviation: IM, intramuscular.

antipsychotics, it is necessary to study these parameters in patients who have not been receiving antipsychotics for a certain period. However, all patients in this study were receiving regular treatment with antipsychotics and were receiving a second antipsychotic to manage episodes of agitation. To a certain extent, it was possible to investigate and compare the differences among the antipsychotics in terms of efficacy and safety because the study was carried out in a common clinical setting and because there were no differences in the chlorpromazine equivalent dose among the antipsychotics administered to each group.

Limitations

This was a short-term study (2 hours) with a relatively small sample size, and it was an open-label, rather than a double-blind study. Thus, it is possible that bias was introduced to the results. Consequently, limited conclusions can be drawn from the results. Since the doses of IM olanzapine and IM levomepromazine that were used in this study were not equivalent, we cannot rule out the possibility that this affected the results.

The greatest limitation of this study was that the patients received IM olanzapine or IM levomepromazine while being treated concomitantly with antipsychotic medications, and we cannot completely rule out these drugs affecting the results of this study. Therefore, a double-blind, randomized, and controlled study on subjects, who are not taking concomitant medication, is necessary to clarify differences in the efficacy and safety of IM olanzapine, IM levomepromazine, and other first-generation injectable formulations.

Conclusion

This study was a comparative investigation of the clinical efficacy and safety of IM olanzapine and IM levomepromazine in agitated elderly patients with schizophrenia. The results of this study suggest that agitated elderly patients rapidly respond to IM olanzapine and IM levomepromazine treatment. Furthermore, these results suggest that IM olanzapine is safer than IM levomepromazine and causes greater improvement in positive symptoms.

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Disclosure

The authors report no conflicts of interest in this work.

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