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

Hide Nobu Suzuki, Keishi Gen and Yuki Takahashi

Abstract

Objective: This study was a comparative investigation of the clinical efficacy and safety of intramuscular (IM) olanzapine and IM haloperidol in agitated elderly patients with schizophrenia at 2 hours postdose.

Methods: The subjects were 23 inpatients who had been diagnosed with schizophrenia according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV). Their clinical symptoms were assessed using Positive and Negative Syndrome Scale Excited Component (PANSS-EC), PANSS and Agitation Calmness Evaluation Scale (ACES), and their safety were assessed using the Abnormal Involuntary Movement Scale (AIMS), Barnes Akathisia Rating Scale (BARS), Drug-Induced Extrapyramidal Symptoms Scale (DIEPSS) and laboratory tests.

Results: The mean reduction from baseline on the PANSS-EC total score, the PANSS total score and the ACES score were significantly greater in the IM olanzapine injection group than in the IM haloperidol injection group. The mean changes from baseline on the AIMS score, the BARS score and the DIEPSS total score were significantly better in the IM olanzapine injection group than in the IM haloperidol injection group. No serious adverse events such as paralytic ileus, diabetic ketoacidosis, neuroleptic malignant syndrome or tardive dyskinesia occurred between the two groups.

Conclusion: The results of this study suggest the possibility that agitated elderly patients may result in superior efficacy and safety after IM olanzapine without serious adverse events in comparison with IM haloperidol.

Keywords: elderly schizophrenia, efficacy, intramuscular haloperidol, intramuscular olanzapine, safety

Introduction

One of the characteristics of acute-stage schizophrenia is that patients are often in an agitated state (e.g. irritable, excited) and sometimes exhibit animosity as well. There may also be worsening of positive symptoms, emotional changes and worsening of catatonia. The most important treatment for these acute symptoms is to promptly control the aggression and acute agitation that the patients frequently exhibit [American Psychiatric Association, 1997; Sharif, 1998; Welch, 1993].

Elderly patients generally have reduced liver and kidney function, are more susceptible to adverse

drug reactions, and are more likely to experience a reduction in their activities of daily living (ADL) and in their quality of life (QOL) as a result of drug-induced adverse drug reactions. In elderly patients with schizophrenia, moreover, a decreased capacity for reality testing combined with a lack of insight make such patients more likely to lose their medication or make mistakes when taking their medication, resulting in severely inadequate treatment adherence. As a result, psychiatric symptoms occasionally become unstable and acute-stage symptoms emerge. Therefore, when using drug therapy in elderly schizophrenia patients, it is important to select a

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drug that not only will be taken reliably, but that also has a superior adverse reaction profile, and to initiate therapy soon after the onset of acute-stage symptoms so that no higher a dose than is necessary is used.

Until now, injectable formulations of atypical antipsychotics have not been used in the clinical setting in Japan; either intramuscular (IM) or intravenous formulations of typical antipsychotics and/or benzodiazepines have normally been chosen [Hirata and Ichie, 2006; Ono *et al.* 2008; Otsuka *et al.* 2006]. However, injectable formulations of typical antipsychotics are clinically problematic in that they can result in akathisia, acute dystonia, neuroleptic malignant syndrome or electrocardiographic (ECG) abnormalities, including QTc interval prolongation [Buckley and Shanders, 2000; Casey, 1995; Hatta *et al.* 2001; Keck *et al.* 1989; Putten and Marder, 1987; Reilly *et al.* 2000]. Injectable formulations of benzodiazepines are clinically problematic in that they can result in respiratory depression [Forster *et al.* 1980; Hatta *et al.* 1998].

Against this background, IM olanzapine has been approved in more than 70 countries worldwide and has become one of the drugs of first choice in early-stage therapy in which parenteral drug therapy is required [Allen *et al.* 2005; American Psychiatric Association, 2004]. IM olanzapine is a drug that has basically the same pharmacokinetics as oral olanzapine. The main difference compared with the oral formulation is that, since absorption is rapid following IM administration, the time to effect onset is shorter [Bergstrom *et al.* 1999]. In December 2012, IM olanzapine came on the market in Japan.

However, there have not been any reports in Japan clarifying the efficacy and safety of IM olanzapine and IM haloperidol in agitated elderly patients with schizophrenia. In this study, we investigated the clinical efficacy and safety of IM olanzapine and IM haloperidol in agitated elderly patients with schizophrenia.

Methods

Subjects

The subjects were 23 patients who were being treated on an inpatient basis at the psychiatry departments of Tanzawa Hospital and had been diagnosed with schizophrenia according to the

Diagnostic and Statistical Manual of Mental Disorders (DSM-IV). Elderly schizophrenia patients (age >60 years) with persistence of symptoms receiving antipsychotic monotherapy were enrolled into this study. Inclusion criteria were: all patients had a total score of 14 or higher on the Positive and Negative Syndrome Scale Excited Component (PANSS-EC) and it was concluded by the treating psychiatrist that the patient needed to be treated with an IM injection; all patients were able to provide informed consent or cooperate with the requirements of the study; and patients had been treated with a stable dose of an oral antipsychotic drug monotherapy for at least 3 months. Exclusion criteria were: patients exhibiting allergic reactions or resistance to olanzapine or haloperidol; and patients with serious internal medicine comorbidities. Patients meeting the following concomitant therapy criteria were excluded from this study in order to clarify the difference in the efficacy of IM olanzapine and IM haloperidol: patients receiving oral olanzapine or haloperidol; and patients receiving benzodiazepine receptor agonists within 4 hours prior to IM administration. The IM olanzapine injection group (12 subjects) and the IM haloperidol injection group (11 subjects) were recruited separately. There were no other medications besides the study antipsychotic.

The study was a nonrandomized, not double-blind, open-labeled, flexible dose, naturalistic observational trial of schizophrenia patients who required an addition to their medication because of acute agitation. The IM olanzapine injection group did not differ in having side effects or symptoms compared with the IM haloperidol injection group. Until November 2012, most patients were receiving the IM haloperidol injection (2.5 or 5.0 mg) and until January 2013, the IM olanzapine injection (5.0, 7.5 or 10.0 mg).

This study adhered to the Declaration of Helsinki and received the necessary official approval to be conducted at each hospital site. Only patients who had provided voluntary informed consent in writing to participate in this study on receiving a full explanation of its purpose and method were enrolled, while patient confidentiality was afforded all due consideration, as were ethical considerations.

Assessment methods

The following clinical assessments were performed at baseline and 2 hours after IM administration by the psychiatrist who was providing the

actual therapy. Therefore, the evaluator was not blind to the patient's treatment. There were no reliability tests for those who applied PANSS-EC [Kay and Sevy, 1990], the Positive and Negative Syndrome Scale (PANSS) [Kay *et al.* 1987], the Agitation Calmness Evaluation Scale (ACES), a single-item, 9-point scale (e.g. 1 = marked agitation, 4 = normal behavior, 9 = unarousable) (Copyright © 1998, Eli Lilly and Company; all rights reserved), the Abnormal Involuntary Movement Scale (AIMS) [Rush, 2000], the Barnes Akathisia Rating Scale (BARS) [Barnes, 1989] and the Drug-Induced Extrapyramidal Symptoms Scale (DIEPSS) [Inada, 1996; Inada *et al.* 1996]. However, assessor training was provided to ensure a certain degree of reliability. The efficacy outcome was the change in the PANSS score and the change in the ACES score. Meanwhile, AIMS, BARS, DIEPSS, vital signs (pulse and blood pressure) and glucose level were used to investigate safety.

Statistical analysis

Three types of statistical analysis were performed:

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

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

Results

There was no difference in background characteristics between the IM olanzapine injection group and the IM haloperidol injection group (Table 1).

The mean reduction from baseline on the PANSS-EC total score, the PANSS total score and the ACES score were significantly greater in

the IM olanzapine injection group than in the IM haloperidol injection group (Table 2, Figure 1). The PANSS positive score decreased significantly from baseline in both the IM olanzapine injection group and the IM haloperidol injection group, but no significant differences were seen between the two groups (Table 2, Figure 1).

The mean changes from baseline on the AIMS score, the BARS score and the DIEPSS total score were significantly better in the IM olanzapine injection group than in the IM haloperidol injection group (Table 2, Figure 1).

The pulse rate decreased from baseline in the IM olanzapine injection group. However, the mean changes from baseline on the pulse rate hardly changed in the IM haloperidol injection group (Table 2). The systolic blood pressure increased significantly from baseline in the IM olanzapine injection group, but the mean change from baseline on the systolic blood pressure hardly changed in the IM haloperidol injection group. The glucose level (mg/dl) decreased significantly from baseline in both the IM olanzapine injection group and the IM haloperidol injection group, but no significant differences were seen between the two groups (Table 2).

The incidence of adverse events associated with injection site reactions in both groups were 16.7% (2/12) in the IM olanzapine injection group and 18.2% (2/11) in the IM haloperidol injection group. All these adverse events were injection site pain; no redness, swelling or induration were observed. The most frequent adverse events in both groups are shown in Table 3.

The injections were administered at the same time in each group. The average medication doses of both groups were 7.7 ± 2.5 (mg) with the IM olanzapine injection group and 4.6 ± 1.0 (mg) with the IM haloperidol injection group.

Discussion

In this study, we compared the efficacy and safety of IM olanzapine and IM haloperidol in agitated elderly patients with schizophrenia at 2 hours postdose.

The results of this study not only show that olanzapine has a different pharmacological profile to haloperidol, but also suggest that IM olanzapine can, thanks to its pharmacokinetics, afford patients

Table 1. Subject characteristics

Characteristic	IM olanzapine group (<i>n</i> = 12)	IM haloperidol group (<i>n</i> = 11)	<i>p</i> value
Age years (mean ± SD)	65.1 ± 7.9	63.8 ± 1.8	0.36
Gender (M : F), <i>n</i> (%)	4 (33.3) : 8 (66.7)	4 (36.4) : 7 (63.6)	0.89
Duration of illness (years (mean ± SD)	42.6 ± 6.3	41.3 ± 4.8	0.58
Chlorpromazine equivalents dose (mg/day) (baseline) (mean ± SD)	493.8 ± 140.3	488.6 ± 193.4	0.94
Biperiden equivalents dose (mg/day) (baseline) (mean ± SD)	1.5 ± 1.8	1.4 ± 1.5	0.85
Diazepam equivalents dose (mg/day) (baseline) (mean ± SD)	6.5 ± 7.0	12.4 ± 13.7	0.20
ACES score (baseline) (mean ± SD)	2.7 ± 0.5	2.7 ± 0.5	0.77
PANSS total score (baseline) (mean ± SD)	97.9 ± 6.9	101.8 ± 11.5	0.33
PANSS-EC score (baseline) (mean ± SD)	17.0 ± 2.7	18.4 ± 1.5	0.15
AIMS total score (baseline) (mean ± SD)	7.2 ± 3.0	6.5 ± 3.6	0.61
BARS total score (baseline) (mean ± SD)	0.8 ± 1.4	0.3 ± 0.9	0.34
DIEPSS total score (baseline) (mean ± SD)	7.6 ± 3.4	8.2 ± 3.5	0.68

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

a more rapid sedative effect and more rapid improvement in impulse control and excitement than IM haloperidol. However, since both drugs possess affinity for dopamine (D2) receptors, no significant difference was found between the two groups in improvement in positive symptoms. The results were therefore consistent with the results of our previous research and the results of other studies conducted in the past [Centorrino *et al.* 2007; MacDonald *et al.* 2012; San *et al.* 2006; Wright *et al.* 2001].

The results suggested that IM olanzapine prevented the emergence of drug-induced extrapyramidal symptoms in the elderly compared with IM haloperidol. The findings also are consistent with those of previously conducted research [Perrin *et al.* 2012; Satterthwaite *et al.* 2008].

In the elderly, arrhythmias result in symptoms including dizziness, palpitations and shortness of breath that are a contributing factor for a poor prognosis. Although the results of this study showed that IM olanzapine resulted in a decrease in pulse rate, it remained within the range of normal in all the subjects. The results of this study therefore show that IM olanzapine had a small effect on pulse rate. Hypertension is a risk factor for cardiovascular disease. Furthermore, in the elderly, hypotension is accompanied by

lightheadedness, and therefore increases the risk of falls and bone fractures. Although the results of this study showed that IM olanzapine resulted in an increase in blood pressure, it remained within the range of normal in all the subjects. The results of this study therefore show that IM olanzapine had a small effect on blood pressure. Treatment with olanzapine may result in fatal outcomes due to diabetic ketoacidosis, diabetic coma, etc. because of a marked increase in the glucose level. Consistent with the results of previous research, the results of this study found that IM olanzapine did not result in an increase in the glucose level to the extent seen with IM haloperidol, and suggested that IM olanzapine may have little effect on the glucose level. Most adverse events were rated mild or moderate. Furthermore, in this study, no serious adverse events such as paralytic ileus, diabetic ketoacidosis, neuroleptic malignant syndrome or tardive dyskinesia occurred.

Limitations

This study had a relatively small sample size and was a short-term study (2 hours). Furthermore it was an open-label and not a double-blind study, so the possibility that bias was introduced to the results cannot be ruled out. There are consequently limits to the conclusions that can be drawn from this study. Since the doses of IM

Table 2. Efficacy and safety.

	IM olanzapine group (<i>n</i> = 12)				IM haloperidol group (<i>n</i> = 11)				<i>F</i> value ^{\$}	<i>p</i> 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	2.7	0.5	1.8	1.0*	2.7	0.5	0.5	0.5**	17.21	0.0005
PANSS										
Total	97.9	6.9	-7.4	1.7*	101.8	11.5	-5.4	1.6*	8.84	0.0073
Positive	23.9	3.7	-3.7	1.4*	24.5	2.9	-2.9	1.0*	0.27	0.61
Negative	27.1	3.6	-	-	28.6	5.2	-	-	-	-
General psychopathology	46.9	2.4	-3.8	0.5*	48.7	6.4	-2.5	1.2*	7.19	0.014
PANSS-EC	17.0	2.7	-5.8	1.8*	18.4	1.5	-3.1	0.8*	9.24	0.006
AIMS total score	7.2	3.0	-0.3	0.9	6.5	3.6	1.5	1.8	8.37	0.0087
BARS total score	0.8	1.4	-0.4	0.9	0.3	0.9	1.5	2.0	8.50	0.0083
DIEPSS total score	8.0	2.8	-0.4	0.7	7.8	2.9	1.5	0.8	28.76	<0.0001
Pulse rate	81.6	8.9	-4.5	8.1	65.7	14.2	-0.3	8.0	1.95	0.18
Systolic blood pressure (mmHg)	117.9	14.0	5.6	8.8	126.4	16.3	-0.2	15.7	2.23	0.15
Diastolic blood pressure (mmHg)	75.2	10.9	-1.8	7.5	74.4	0.7	-0.5	12.9	0.16	0.70
Glucose (mg/dl)	118.1	37.5	-7.2	5.6*	107.1	23.9	-11.4	15.0**	0.67	0.42

p* < 0.005 versus baseline; *p* < 0.05 versus baseline; \$Repeated measures analysis of variance (ANOVA): the groups (IM olanzapine group and IM haloperidol group) × time interaction (at baseline and 2 hours after IM administration) of each rating scale.
ACES, Agitation Calmness Evaluation Scale; AIMS, Abnormal Involuntary Movement Scale; BARS, Barnes Akathisia Rating Scale; DIEPSS, Drug-Induced Extrapyramidal Symptoms Scale; IM, intramuscular; PANSS, Positive and Negative Syndrome Scale; PANSS-EC, Positive and Negative Syndrome Scale Excited Component; SD, standard deviation.

p* < 0.005 versus baseline; *p* < 0.05 versus baseline; \$Repeated measures analysis of variance (ANOVA): the groups (IM olanzapine group and IM haloperidol group) × time interaction (at baseline and 2 hours after IM administration) of each rating scale.

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

Figure 1. Efficacy and safety.

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

Table 3. Adverse events.

	Number (%) of patients	
	IM olanzapine group (n = 12)	IM haloperidol group (n = 11)
Bradycardia	0	2 (18.2)
Blood pressure increased	3 (25.0)	2 (18.2)
Low blood pressure	0	1 (9.1)
Somnolence	2 (16.7)	0
Susceptibility dizziness	2 (16.7)	0
Thirst	1 (8.3)	0
Agitation	0	2 (18.2)
IM, intramuscular.		

olanzapine and IM haloperidol used in this study were not equivalent, we cannot rule out the possibility that this affected the study results. Furthermore, because only those patients who could give informed consent in this study were included, there is a limit to the results of this study. The greatest problem with this study is that the patients received IM olanzapine or IM haloperidol while being treated concomitantly with antipsychotic medications, and it is therefore

impossible to completely rule out the possibility that the antipsychotic drugs that the patients were receiving affected the results of this study. A double-blind, randomized, controlled study in subjects who are not taking concomitant medication potentially affecting efficacy and safety may be necessary in the future to clarify the differences in efficacy and safety between IM olanzapine, IM haloperidol and other first-generation injectable formulations.

Conclusion

This study was a comparative investigation of the clinical efficacy and safety of IM olanzapine and IM haloperidol in agitated elderly patients. The results of this study suggest the possibility that agitated elderly patients may result in superior efficacy and safety after IM olanzapine without serious adverse events in comparison with IM haloperidol.

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Conflict of interest statement

H.S. received honoraria from Janssen, Otsuka and Dainippon Sumitomo. K.G. received a honoraria from Janssen. Y.T. received honoraria from Otsuka.

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