ORIGINAL ARTICLE

A Double-blind, Placebo-Controlled Dose-Response Comparison of Intramuscular Olanzapine and Haloperidol in the Treatment of Acute Agitation in Schizophrenia

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Background: An intramuscular (IM) formulation of olanzapine has been developed because there are no rapid-acting IM atypical antipsychotic drugs currently available in the United States for treating acute agitation in patients with schizophrenia.

Methods: Recently hospitalized acutely agitated patients with schizophrenia (N=270) were randomized to receive 1 to 3 IM injections of olanzapine (2.5, 5.0, 7.5, or 10.0 mg), haloperidol (7.5 mg), or placebo within 24 hours. A dose-response relationship for IM olanzapine in the reduction of agitation was assessed by measuring the reduction in Positive and Negative Syndrome Scale Excited Component (PANSS-EC) scores 2 hours after the first injection. Safety was assessed by recording adverse events and with extrapyramidal symptom scales and electrocardiograms at 24 hours after the first injection.

Results: Olanzapine exhibited a dose-response relationship for reduction in agitation ($F_{1,179}=14.4$; $P<.001$). Mean PANSS-EC reductions 2 hours after the first injection of olanzapine (2.5 mg=–5.5; 5.0 mg=–8.1; 7.5 mg=–8.7; 10.0 mg=–9.4) were superior to those with placebo (–2.9; $P=.01$ vs olanzapine at 2.5 mg; $P<.001$ for each other olanzapine dose) but not with haloperidol (–7.5). A dose of 5.0, 7.5, or 10.0 mg of olanzapine caused a greater reduction in agitation than placebo 30 minutes after the first injection. There were no differences between treatment groups for hypotension, the most frequently reported adverse event, or for clinically relevant changes in the QTc interval. There was a greater incidence of treatment-emergent parkinsonism during treatment with IM haloperidol (16.7%) than with 2.5 ($P=.03$), 5.0 ($P=.03$), or 7.5 mg ($P=.01$) of IM olanzapine (0%) or with placebo (0%) ($P=.01$).

Conclusions: Intramuscular olanzapine at a dose of 2.5 to 10.0 mg per injection exhibits a dose-response relationship in the rapid treatment of acute agitation in patients with schizophrenia and demonstrates a favorable safety profile.

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ACUTE AGITATION is common in patients with schizophrenia and may be accompanied by destructive and/or violent behavior.[1-3] Rapid treatment with intramuscular (IM) typical antipsychotic and/or benzodiazepine agents may be essential to prevent injury to the patient or others.[4,5] However, IM typical antipsychotics are associated with acute dystonia,[6,7] akathisia,[8] neuroleptic malignant syndrome,[9] and electrocardiographic (ECG) abnormalities including prolongation of the QTc interval.[10,11] Intramuscular benzodiazepines may cause excessive sedation leading to respiratory depression,[12-15] ataxia, and confusion.[16] These adverse events present a greater risk when typical antipsychotic agents and benzodiazepines are administered together and/or intravenously.[17-20]

An IM formulation of an atypical antipsychotic agent may present several treatment advantages when rapid treatment of acute agitation is essential in patients with schizophrenia. Atypical antipsychotic agents are significantly less likely to cause extrapyramidal symptoms than typical antipsychotic agents.[21-23] In addition, some atypical agents (eg, olanzapine and risperidone), but not all (sertindole or ziprasidone [Pfizer Pharmaceuticals, New York, NY, unpublished data, 2000]), have a more favorable ECG safety profile than specific (eg, thioridazine or droperidol), but not all (haloperidol), typical antipsychotic agents.[10,22-24] Furthermore, oral atypical antipsychotic agents are widely used for long-term maintenance therapy, and an IM atypical antipsychotic agent may therefore facilitate the transition to oral atypical maintenance therapy.[25]

This study tested the a priori primary hypothesis that 2.5, 5.0, 7.5, and 10.0 mg per injection of IM olanzapine would exhibit a dose-response relationship in reducing agitation in patients with schizophre-

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SUBJECTS AND METHODS

Recently hospitalized patients 18 years or older who had been clinically diagnosed by the study investigators as having schizophrenia, schizophreniform disorder, or schizoaffective disorder (according to the *DSM-IV*[31]) were recruited by the site investigators based on their suitability as defined by inclusion and exclusion criteria. All patients had a total score of 14 or higher (of a maximum of 35) on the PANSS-EC with a score of 4 or higher (of a maximum of 7) on at least 1 item and were acutely agitated to the extent that parenteral antipsychotic therapy was warranted. However, patients were not so agitated that they were unable to provide informed consent or cooperate with the requirements of the study. Thus, patients were physically and verbally overactive and were occasionally hostile, destructive to property, or threatening, but no patient required physical restraint or was violent toward other individuals. Patients with significant medical disorders, including alcohol and/or drug dependency, were excluded from this trial.

The study was conducted at 4 sites in Croatia (69 patients), 1 in Italy (3 patients), 3 in Romania (82 patients), and 6 in South Africa (116 patients). The study protocol was approved by local ethical review boards. The review boards approved the use of placebo given the hospitalized status of all participating patients, the 5:1 randomization ratio for active treatment vs placebo, the brief duration of the study (24 hours), and the use of active medication based on the clinical judgment of the investigator at the time of randomization. Written informed consent was obtained from all patients and from a relative or legal representative when required by local law or custom.

PROCEDURE

The study consisted of a screening period and a 24-hour IM treatment period. Patients were not allowed to receive any antipsychotic treatment during the screening period, which lasted for a minimum of 2 hours. On entering the treatment period, patients were randomly allocated to treatment with 2.5, 5.0, 7.5, or 10.0 mg per injection of IM olanzapine, 7.5 mg per injection of IM haloperidol, or IM placebo by the assignment of treatment kits. The doses of IM olanzapine were based on data from 2 previous open-label pilot clinical trials (N=118) in which doses from 2.5 to 10.0 mg were found to be safe and effective.[32,33] Intramuscular haloperidol was chosen for comparison because it is the most frequently used IM antipsychotic worldwide for treating acute agitation in patients with schizophrenia.[34]

Patients could receive a maximum of 3 injections within the 24-hour treatment period. Second and third injections were administered at the discretion of the investigator, as clinically indicated. The second injection was allowed after 2 hours had passed since the first injection, and a third injection was allowed after 4 hours had elapsed since the second injection, with both to have been administered within 20 hours after the first injection. All investigators, raters, clinical staff involved with patient care, and patients were kept blind to treatment assignment throughout the study. To ensure blinding, unblinded third-party personnel, who played no role in evaluating patients, were trained to handle and administer injections in identical, unmarked syringes.

Concomitant treatment with alpidem, anorectics, antiemetics, antiarrythmics, carbamazepine, methyldopa, neuroleptics, phenobarbital, reserpine, or zolpidem tartrate was prohibited during the study. Concomitant treatment with benzodiazepines was prohibited from 4 or more hours before until 3 or more hours after administration of the first injection. Thereafter, patients who received 1, 2, or 3 injections of the study drug were permitted to receive 0, 1, or 2 benzodiazepine doses, respectively (2-4 mg of lorazepam [IM or oral], 10-20 mg of diazepam [IM, intravenous, or oral], 10-30 mg of oxazepam [oral], or 5-50 mg of clorazepate [IM or oral]), each dose being administered 1 or more hours after the previous injection of the study drug. Anticholinergic medication was permitted for the treatment of newly emergent extrapyramidal symptoms, but prophylactic use was prohibited.

ASSESSMENTS

Efficacy

Patients were assessed by the study investigators (14 investigators, all of whom underwent training and interrater reliability testing) at the screening visit, immediately prior to and at 30, 60, and 90 minutes and 2, 4, 6, 12, and 24 hours after the first injection. The primary efficacy measure was the PANSS-EC, which includes the items

nia, as measured by the mean change on the Positive and Negative Syndrome Scale Excited Component (PANSS-EC)[26] from the time of first injection until 2 hours later. This study also tested the following secondary hypotheses: (1) IM olanzapine would be superior to IM placebo in reducing acute agitation and no different from 7.5 mg of IM haloperidol at 2 hours after the first injection; (2) the efficacy of IM olanzapine in reducing agitation would be confirmed by measuring response rates, benzodiazepine use, and injection frequency and by the use of additional rating scales for agitation and general psychiatric status; (3) the efficacy of IM olanzapine would be sustained for a clinically useful period (24 hours); and (4) IM olanzapine would have a better overall safety profile than IM haloperidol. The dose of 7.5 mg of IM haloperidol was chosen based on the literature[20,27-29] and clinical experience indicating that both 5.0-mg and 10.0-mg doses are commonly used to treat acute agitation; thus, 7.5 mg represents a compromise between these doses. In addition, a dose-response analysis suggests that escalating doses up to 7.5 mg results in an incremental enhancement of efficacy, but doses that exceed 7.5 mg to 10.0 mg do not appreciably increase immediate efficacy for most patients and may cause additional adverse effects.[30]

RESULTS

PATIENT CHARACTERISTICS AND DISPOSITION

Most of the 270 patients (IM olanzapine: n=48 for 2.5 mg, n=45 for 5.0 mg, n=46 for 7.5 mg, and n=46 for 10.0 mg; IM haloperidol: n=40; IM placebo: n=45) who participated in this study were white (65.9%) men (57.4%), with ages ranging from 18 to 73 years (mean±SD age, 36.3±10.7

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tension, uncooperativeness, hostility, poor impulse control, and excitement and was derived from the PANSS by its originators using a principal-components factor analysis.[26] The PANSS-EC was chosen as the primary efficacy measure because (1) it has high face validity in the measurement of agitation; (2) data from agitated and nonagitated patients who had participated in a registration trial of oral olanzapine (n=1996) provided confirmatory validation of the PANSS-EC (Eli Lilly and Company, Indianapolis, Ind, unpublished data, 1997); and (3) it is rated by physician observation 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. The validity of each PANSS-EC recording was ensured by requiring investigators to read PANSS-EC item descriptors and complete separate record pages at each evaluation.

Agitation was further assessed with the Agitated Behavior Scale (ABS)[35] and the Agitation Calmness Evaluation Scale (ACES) (Copyright 1998, Eli Lilly and Company; all rights reserved), a single-item scale developed by Eli Lilly and Company on which 1 indicates marked agitation; 2, moderate agitation; 3, mild agitation; 4, normal; 5, mild calmness; 6, moderate calmness; 7, marked calmness; 8, deep sleep; and 9, unable to be aroused. The PANSS-derived Brief Psychiatric Rating Scale (BPRS) and Clinical Global Impressions–Severity (CGI-S) scale[36] were used to assess general psychiatric status.

Safety

During the 24-hour treatment period, safety was assessed by clinical examination and laboratory investigations, recording spontaneously reported adverse events, completing the Simpson-Angus[37] and Barnes Akathisia Scales,[38] and recording ECGs during screening or immediately prior to the first IM injection and at 2 and 24 hours after the first IM injection. The ECG QT interval correction formula was $QTc = QT/RR^{1/2}$.

STATISTICAL METHODS

A dose-response relationship on the PANSS-EC at 2 hours after the first IM injection was investigated across IM olanzapine treatment groups using a linear trend test with contrast coefficients of −3, −1, 1, and 3 for IM olanzapine at 2.5 mg, 5.0 mg, 7.5 mg, and 10.0 mg, respectively.

Comparisons among IM olanzapine treatment groups, between IM olanzapine and IM placebo groups, and between IM olanzapine and IM haloperidol groups were performed using analysis of variance models (raw data) that took into account treatment and country. The analysis was not planned a priori to assess investigator site effects, although these were performed post hoc. Adjustments for multiple comparisons were not performed for the pairwise comparisons. Comparisons between treatment groups at each of the 30-, 60-, and 90-minute assessment times were also performed.

Response was defined a priori as a 40% reduction or more in PANSS-EC score from baseline to 2 hours after the first IM injection because open-label studies showed that a 40% PANSS-EC score reduction reasonably represented the rapid, substantial, and sustained reduction in agitation desired when an IM antipsychotic is administered.[32,33] Response rates were compared across all treatment groups using the stratum-adjusted Pearson χ^2 test (Cochran-Mantel-Haenszel option; SAS statistical software version 6.08 [SAS Institute Inc, Cary, NC]) controlling for country. Pairwise comparisons were also performed using the Cochran-Mantel-Haenszel statistic,[39] stratifying by country, and the Breslow-Day test[40] to investigate the homogeneity of odds ratios across countries. A dose-response relationship for response rates was investigated using the extended Mantel-Haenszel correlation statistic,[41] stratifying by country.

Categorical data (demographic variables, reasons for study discontinuation, treatment-emergent adverse events, incidence of benzodiazepine and anticholinergic use, and potentially clinically significant ECGs) were evaluated in a pairwise fashion using the Fisher exact test. The incidence of treatment-emergent parkinsonism (the proportion of patients with a Simpson-Angus Scale total score >3 during the 24-hour IM period among those with a total score ≤3 at baseline) and treatment-emergent akathisia (the proportion of patients with a Barnes Akathisia Scale global score [item 4] ≥2 during the 24-hour IM period among those with a score <2 at baseline) were evaluated in a pairwise fashion using the Fisher exact test. To determine whether there was an association between treatment and number of IM injections received (1, 2, or 3), a Cochran-Mantel-Haenszel test was performed stratifying by country. All hypothesis tests were performed using 2-tailed tests.

years) and a mean ± SD age at onset of illness of 25.1 ± 7.3 years. There were no treatment group differences at baseline for any patient characteristics (**Table 1**).

Almost all patients (268 or 99.3%) completed the 24-hour IM treatment period. Two patients (0.7%) receiving 5.0 mg of IM olanzapine discontinued treatment (lack of efficacy; physician decision), but both were included in efficacy and safety analyses because postbaseline data were collected on these individuals.

EFFICACY

PANSS-EC Change From Time of First Injection Until 2 Hours Later

A monotonic dose-response relationship existed across the IM olanzapine dose range ($F_{1,179} = 14.4$; $P < .001$). All IM olanzapine doses and 7.5 mg of IM haloperidol were superior to IM placebo in reducing agitation, but IM olanzapine at 2.5 mg was less effective than any of the other IM olanzapine doses or IM haloperidol (**Table 2**). Patients treated with 5.0, 7.5, or 10.0 mg of IM olanzapine had greater mean improvement than those given IM placebo at all time points (**Figure**). The groups given 2.5 mg of IM olanzapine or IM haloperidol did not show greater mean improvement compared with those given IM placebo until 60 minutes after the first injection.

There was a monotonic dose-response relationship across the IM olanzapine dose groups ($\chi^2_1 = 12.0$; $P < .001$) for PANSS-EC response rates 2 hours after the first IM injection. Greater response rates were observed with IM olanzapine at 2.5 mg (50.0%; $\chi^2_1 = 9.1$; $P = .003$), 5.0 mg (62.6%; $\chi^2_1 = 16.7$; $P < .001$), 7.5 mg (73.9%; $\chi^2_1 = 26.5$; $P < .001$), and 10.0 mg (80.4%; $\chi^2_1 = 34.4$; $P < .001$) and with IM halo-

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Table 1. Patient Characteristics at Baseline*

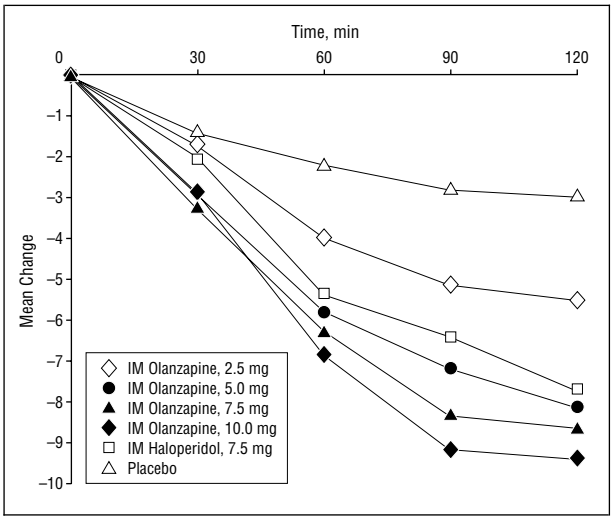
Characteristic	Treatment: IM Olanzapine, 2.5 mg (n = 48)	IM Olanzapine, 5.0 mg (n = 45)	IM Olanzapine, 7.5 mg (n = 46)	IM Olanzapine, 10.0 mg (n = 46)	IM Haloperidol, 7.5 mg (n = 40)	IM Placebo (n = 45)
Age, mean ± SD, y	36.2 ± 10.5	35.1 ± 10.1	35.9 ± 11.3	36.7 ± 12.1	37.4 ± 10.6	36.7 ± 10.3
Age at onset, mean ± SD, y	25.0 ± 6.5	23.9 ± 7.6	25.9 ± 7.4	25.3 ± 8.1	25.9 ± 6.9	24.9 ± 7.7
Sex: M	31 (64.6)	27 (60.0)	26 (56.5)	26 (56.5)	22 (55.0)	23 (51.1)
Race						
White	29 (60.4)	31 (68.9)	29 (63.0)	32 (69.6)	25 (62.5)	32 (71.1)
African	11 (22.9)	11 (24.4)	12 (26.1)	11 (23.9)	12 (30.0)	8 (17.8)
Western Asian	2 (4.2)	0	0	0	0	2 (4.4)
Other	6 (12.5)	3 (6.7)	5 (10.9)	3 (6.5)	3 (7.5)	3 (6.7)

*Data are presented as number (percentage) unless otherwise indicated. IM indicates intramuscular; sample size, number of patients with a baseline and at least 1 postbaseline measurement within the stated period.

Table 2. Mean PANSS-EC Score Change From Baseline to 2 Hours After the First IM Injection (LOCF)*

Therapy	Sample Size	Baseline, Mean (SD)	Change, Mean (SD)	*t*†; *P*: vs IM Olanzapine, 5.0 mg	vs IM Olanzapine, 7.5 mg	vs IM Olanzapine, 10.0 mg	vs IM Haloperidol, 7.5 mg	vs IM Placebo
IM olanzapine, 2.5 mg	n = 48	18.3 (2.4)	−5.5 (4.6)	2.6; .01	3.2; .001	3.8; <.001	2.0; .04	2.6; .01
IM olanzapine, 5.0 mg	n = 45	19.7 (3.4)	−8.1 (5.3)	. . .	0.6; .55	1.1; .26	0.5; .63	5.1; <.001
IM olanzapine, 7.5 mg	n = 46	18.9 (2.6)	−8.7 (5.0)	. . .	. . .	0.5; .60	1.1; .28	5.7; <.001
IM olanzapine, 10.0 mg	n = 46	19.3 (2.6)	−9.4 (4.9)	. . .	. . .	. . .	1.6; .12	6.3; <.001
IM haloperidol, 7.5 mg	n = 40	19.3 (3.1)	−7.5 (5.9)	. . .	. . .	. . .	. . .	4.5; <.001
IM placebo	n = 45	18.8 (2.8)	−2.9 (4.7)	. . .	. . .	. . .	. . .	. . .

*PANSS-EC indicates Positive and Negative Syndrome Scale Excited Component; IM, intramuscular; LOCF, last observation carried forward; sample size, number of patients with a baseline and at least 1 postbaseline measurement within the stated period; and ellipses, not applicable.
†degrees of freedom = 262.



Mean change in Positive and Negative Syndrome Scale Excited Component score from baseline to each time point within 2 hours after the first intramuscular (IM) injection. For IM olanzapine at 2.5 mg vs IM placebo, $P=.65$ at 30 minutes, $P=.05$ at 60 minutes, $P=.02$ at 90 minutes, and $P=.01$ at 120 minutes. For IM olanzapine at 5.0 mg vs IM placebo, $P=.03$ at 30 minutes and $P<.001$ at 60, 90, and 120 minutes. For IM olanzapine at 7.5 mg vs IM placebo, $P=.007$ at 30 minutes and $P<.001$ at 60, 90, and 120 minutes. For IM olanzapine at 10.0 mg vs IM placebo, $P=.05$ at 30 minutes and $P<.001$ at 60, 90, and 120 minutes. For IM haloperidol at 7.5 mg vs IM placebo, $P=.34$ at 30 minutes and $P<.001$ at 60, 90, and 120 minutes.

peridol (60.0%; $\chi^2_1=15.0$; $P<.001$) than with IM placebo (20.0%). Greater response rates were observed with IM olanzapine at 7.5 mg ($\chi^2_1=5.7$; $P=.02$) and 10.0 mg ($\chi^2_1=10.2$; $P<.001$) than at 2.5 mg, whereas there were no differences between any IM olanzapine dose (including 2.5 mg) and IM haloperidol.

Additional Efficacy Measures

On the ABS, ACES, and BPRS Total and Positive scales, all IM olanzapine and IM haloperidol groups showed greater mean improvement at 2 hours after the first IM injection than the IM placebo group, except IM olanzapine at 2.5 mg on the ACES and IM haloperidol on the BPRS Positive (**Table 3**). Compared with IM haloperidol, greater improvement was observed on the ABS with IM olanzapine at 7.5 mg ($t_{261}=2.4$; $P=.02$) and 10.0 mg ($t_{261}=2.3$; $P=.02$) and on the ACES with IM olanzapine at 10.0 mg ($t_{261}=2.3$; $P=.02$).

At 24 hours after the first IM injection, on the PANSS-EC, ABS, ACES, BPRS Total, and BPRS Positive scales, all IM olanzapine treatment groups showed greater mean improvement than the IM placebo group except IM olanzapine at 2.5 mg on the BPRS Positive ($t_{262}=1.8$; $P=.07$) (**Table 4**). On the CGI-S at 24 hours, patients receiving 5.0 mg ($t_{261}=2.2$; $P=.03$) and 7.5 mg ($t_{261}=3.1$; $P=.003$) of IM olanzapine showed greater improvement

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Table 3. Mean Change From Baseline to 2 Hours After the First IM Injection (LOCF) in Additional Efficacy Measures*

	Change From Baseline to 2 h, Mean (SD)					
Efficacy Measure	IM Placebo (n = 45)	IM Olanzapine, 2.5 mg (n = 48)	IM Olanzapine, 5.0 mg (n = 45)	IM Olanzapine, 7.5 mg (n = 46)	IM Olanzapine, 10.0 mg (n = 46)	IM Haloperidol, 7.5 mg (n = 39)†
BPRS Total	−3.7 (5.5)‡	−8.2 (9.1)#	−10.4 (7.5)	−12.0 (7.0)	−12.0 (5.9)	−9.2 (7.2)§
BPRS Positive	−0.4 (1.3)‡	−1.5 (3.1)	−1.7 (2.8)	−2.1 (2.9)	−1.9 (2.3)	−1.4 (2.2)
ABS	−3.0 (5.0)‡	−5.8 (5.5)¶	−9.0 (5.5)	−10.5 (5.6)‖	−10.4 (5.7)‖	−7.7 (5.2)§
ACES	0.7 (1.2)‡	1.3 (1.5)¶	2.3 (1.9)	2.4 (1.7)	2.6 (1.7)‖	1.8 (1.6)§

*IM indicates intramuscular; LOCF, last observation carried forward; sample size, number of patients with a baseline and at least 1 postbaseline measurement within the stated period; BPRS, Brief Psychiatric Rating Scale; ABS, Agitated Behavior Scale; and ACES, Agitation Calmness Evaluation Scale (Copyright 1998, Eli Lilly and Company; all rights reserved).
†n = 40 for ACES.
‡$P<.05$ vs all IM olanzapine treatment groups, except IM olanzapine at 2.5 mg on the ACES.
§$P<.05$ vs IM placebo.
‖$P<.05$ vs IM haloperidol at 7.5 mg.
¶$P<.05$ vs all other IM olanzapine treatment groups.
#$P<.05$ vs IM olanzapine at 7.5 mg and 10.0 mg.

Table 4. Mean Change From Baseline to 24 Hours After the First IM Injection (LOCF) in Efficacy Measures*

	Change From Baseline to 24 h, Mean (SD)					
Efficacy Measure	IM Placebo (n = 45)	IM Olanzapine, 2.5 mg (n = 48)	IM Olanzapine, 5.0 mg (n = 45)	IM Olanzapine, 7.5 mg (n = 46)	IM Olanzapine, 10.0 mg (n = 46)	IM Haloperidol, 7.5 mg (n = 40)
PANSS-EC	−3.1 (3.3)‡	−4.9 (4.3)	−5.5 (4.9)	−5.5 (4.1)	−5.9 (5.2)	−4.5 (4.0)
BPRS Total†	−4.3 (5.4)‡	−8.4 (7.4)	−9.2 (7.8)	−9.6 (7.5)	−9.0 (7.7)	−7.3 (7.5)
BPRS Positive	−0.6 (2.2)‡	−1.5 (2.3)	−2.0 (2.6)	−1.9 (2.7)	−1.7 (2.4)	−1.8 (3.0)§
ABS	−2.6 (4.0)‡	−5.7 (4.2)	−6.7 (5.9)	−7.7 (5.8)‖	−7.4 (7.0)‖	−5.0 (4.1)§
CGI-S	−0.2 (0.6)	−0.3 (0.5)	−0.5 (0.8)§	−0.6 (0.7)§	−0.4 (0.5)	−0.4 (0.6)
ACES	0.5 (0.7)‡	0.9 (0.8)	1.1 (1.1)	1.0 (1.0)	0.9 (0.9)	0.8 (0.7)

*IM indicates intramuscular; LOCF, last observation carried forward; sample size, number of patients with a baseline and at least 1 postbaseline measurement within the stated period; PANSS-EC, Positive and Negative Syndrome Scale Excited Component; BPRS, Brief Psychiatric Rating Scale; ABS, Agitated Behavior Scale; CGI-S, Clinical Global Impressions–Severity; and ACES, Agitation Calmness Evaluation Scale (Copyright 1998, Eli Lilly and Company; all rights reserved).
†Mean (SD) baseline BPRS Total scores (using 0-6 scoring for each item) were as follows: IM placebo, 35.5 (9.13); IM olanzapine at 2.5 mg, 36.0 (9.0); IM olanzapine at 5.0 mg, 40.0 (9.2); IM olanzapine at 7.5 mg, 37.8 (8.9); IM olanzapine at 10.0 mg, 37.7 (7.3); and IM haloperidol, 37.9 (9.5).
‡$P<.05$ vs all IM olanzapine treatment groups, except IM olanzapine at 2.5 mg on the BPRS Positive.
§$P<.05$ vs IM placebo.
‖$P<.05$ IM haloperidol at 7.5 mg.

than those receiving IM placebo. Intramuscular haloperidol was different from IM placebo at 24 hours on the BPRS Positive ($t_{262}=2.3$; $P=.02$) and ABS ($t_{262}=2.0$; $P=.05$). At 24 hours, patients given the 7.5-mg ($t_{262}=2.5$; $P=.02$) and 10.0-mg ($t_{262}=2.2$; $P=.03$) doses of IM olanzapine showed greater mean improvement on the ABS than those receiving IM haloperidol.

Benzodiazepine Use

During the 24-hour IM treatment period, the incidence of benzodiazepine use was greater during treatment with IM placebo than with any dose of IM olanzapine or IM haloperidol. There were no differences between any of the IM olanzapine dose groups and the IM haloperidol group (**Table 5**).

Dosage Administered and Injection Frequency During the 24-Hour IM Treatment Period

The mean total study medication dosages administered to patients in each group during the 24-hour IM treatment period are shown in Table 5. There was an overall treatment group difference in the proportion of patients receiving 1 to 3 IM injections ($\chi^2_5=54.8$; $P<.001$), with the number of injections different between each active treatment group and the IM placebo group.

SAFETY

Spontaneously Reported Treatment-Emergent Adverse Events During the 24-Hour IM Treatment Period

Overall, the most frequently reported adverse event was hypotension (IM olanzapine at 2.5 mg, 4.2% [2/48 patients]; IM olanzapine at 5.0 mg, 4.4% [2/45 patients]; IM olanzapine at 7.5 mg, 2.2% [1/46 patients]; IM olanzapine at 10.0 mg, 4.3% [2/46 patients]; IM haloperidol, 0% [0/40 patients]; IM placebo, 0% [0/45 patients]), although no between-group differences were observed. Acute dystonia occurred in 0% (0/185 patients) of patients treated with IM olanzapine, 0% (0/45 patients) of

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Table 5. Dosage Administered, Injection Frequency, and Benzodiazepine Use During the 24-Hour IM Treatment Period*

	Treatment					
	IM Placebo	IM Olanzapine, 2.5 mg	IM Olanzapine, 5.0 mg	IM Olanzapine, 7.5 mg	IM Olanzapine, 10.0 mg	IM Haloperidol, 7.5 mg
24-h study drug dosage, mean (SD), mg	. . .	4.0 (1.5)	6.9 (2.7)	9.8 (3.8)	12.6 (4.9)	9.9 (4.6)
Patients receiving 2 or 3 injections, %†	66.7	52.1	35.5	28.3	23.9‡	25‡
Benzodiazepine use, %§	35.6‖	10.4	4.4	4.3	8.7	0
Benzodiazepine dosage, mean (SD), lorazepam equivalents	3.4 (1.1)	3.2 (1.1)	2.0 (0.0)	3.0 (1.4)	3.5 (1.0)	0

*IM indicates intramuscular; ellipses, not applicable.
†The number of injections was significantly different (Fisher exact test; $P<.001$ in all cases) between each active treatment group and placebo.
‡χ^2 test; $P<.05$ vs IM olanzapine at 2.5 mg.
§Benzodiazepines were not permitted until 3 or more hours after the administration of the first injection of the study drug.
‖Fisher exact test; $P<.05$ vs all IM olanzapine treatment groups and IM haloperidol at 7.5 mg.

those receiving IM placebo, and 5.0% (2/40 patients) of those treated with IM haloperidol, with no between-group differences.

Treatment-Emergent Extrapyramidal Symptoms and Anticholinergic Use During the 24-Hour IM Treatment Period

Treatment-emergent parkinsonism was less common in patients treated with IM olanzapine (2.5-7.5 mg, 0% [0/107 patients]; 10.0 mg, 2.9% [1/35 patients]) and IM placebo (0% [0/37 patients]) than with IM haloperidol (16.7% [6/36 patients]), with differences (Fisher exact test) noted between IM haloperidol and IM olanzapine at 2.5 mg ($P=.03$), 5.0 mg ($P=.03$), and 7.5 mg ($P=.01$) and vs IM placebo ($P=.01$). Treatment-emergent akathisia was less common in patients treated with IM olanzapine (2.5 mg, 7.5 mg, and 10.0 mg, 0% [0/129 patients]; 5.0 mg, 4.8% [2/42 patients]) and IM placebo (0% [0/42 patients]) than with IM haloperidol (7.9% [3/38 patients]), although no between-group differences were observed.

Anticholinergic medication was received by 3 patients (7.5%) treated with IM haloperidol and 1 patient (2.1%) treated with 2.5 mg of IM olanzapine, with no between-group differences.

Changes in ECG QTc Intervals During the 24-Hour IM Treatment Period

No patient had an increase in the QTc interval of 500 milliseconds or greater, and there were only small baseline-to-24-hour end point changes in mean±SD QTc intervals, with none being clinically relevant (IM olanzapine at 2.5 mg, −4.3±22.3; IM olanzapine at 5.0 mg, −3.1±23.2; IM olanzapine at 7.5 mg, −2.8±19.6; IM olanzapine at 10.0 mg, −1.9±31.0; IM haloperidol at 7.5 mg, 6.5±24.7; IM placebo, 1.2±21.5). The incidence of potentially clinically significant QTc interval values, based on the sex-specific criteria of a QTc interval of 430 milliseconds or more for men and 450 milliseconds or more for women (IM olanzapine at 2.5 mg, 0% [0/45 patients]; IM olanzapine at 5.0 mg, 9.8% [4/41 patients]; IM olanzapine at 7.5 mg, 4.4% [2/45 patients]; IM olanzapine at 10.0 mg, 7.9% [3/38 patients]; IM haloperidol, 14.3% [5/35 patients]; IM placebo, 19.0% [8/42 patients]), was greater during treatment with IM olanzapine at 5.0 mg ($P=.05$), IM haloperidol ($P=.01$), and IM placebo ($P=.002$) than with IM olanzapine at 2.5 mg and with IM placebo vs IM olanzapine at 7.5 mg ($P=.05$).

COMMENT

This study demonstrated a dose-response relationship for IM olanzapine across the dose range of 2.5, 5.0, 7.5, and 10.0 mg per injection for a reduction in agitation, as measured by changes on the PANSS-EC from the time of first injection until 2 hours afterward. Intramuscular olanzapine at doses of 2.5, 5.0, 7.5, and 10.0 mg and IM haloperidol at 7.5 mg were superior in efficacy on the PANSS-EC compared with IM placebo 2 hours after the first IM injection, and this effect was sustained with IM olanzapine for up to 24 hours. Although hypotension was the most frequently reported treatment-emergent adverse event overall, there were no between-group differences or clinically relevant changes in the QTc interval. Spontaneously reported acute dystonia did not occur in any of the 185 IM olanzapine-treated patients but did occur in 2 of the 40 IM haloperidol-treated patients. Treatment-emergent parkinsonism was more common during treatment with IM haloperidol than with either IM olanzapine or IM placebo.

This study has several limitations. First, it was designed to have sufficient power to detect differences between each dose of active medication and placebo rather than between individual doses of active medication. Second, the study was not designed to recruit adequate numbers of patients at all investigator sites to investigate potential differential treatment effects between sites; however, results from the 6 largest recruiting sites (accounting for 193/270 patients [71.5%]) were consistent with the overall findings comparing each active treatment group with IM placebo. Third, the initial injection of active medication was so efficacious in most patients that a second or third injection was rarely required; thus, there is limited data on repeated dosing, particularly for IM olanzapine at 10.0 mg. Fourth, benzodiazepines were used in this study as described previously, and these may confound the efficacy outcomes. However, benzodiazepine use was limited, and it is likely that any potential

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bias would favor IM placebo because IM placebo-treated patients received significantly more benzodiazepines than IM olanzapine-treated patients. Fifth, a medication history was not collected. Nevertheless, because of the chronic nature of schizophrenia and related disorders, most patients were probably receiving antipsychotic medication. Sixth, *DSM-IV* diagnoses of schizophrenia, schizophreniform disorder, or schizoaffective disorder were determined by the site investigators using all available information; however, structured diagnostic interviews were not obtained. Finally, although the study patients had schizophrenia and were sufficiently agitated to be appropriate candidates for parenteral antipsychotic therapy, they were not so agitated that they were unable to provide informed consent or participate in the clinical trial. Therefore, it will be important to determine if our data generalize to patients who are more agitated than those studied. The moderate level of agitation, the 24-hour duration of the study, and the use of second and third injections and concomitant benzodiazepines probably account for the high completion rates (99.3%).

Doses of 5.0, 7.5, and 10.0 mg of IM olanzapine were superior to IM placebo on the PANSS-EC by 30 minutes after the first IM injection, indicating a rapid onset of effect with these doses. Intramuscular olanzapine also resulted in greater improvement than IM haloperidol on the ABS (7.5 mg and 10.0 mg) and ACES (10.0 mg). In addition, 7.5 mg of IM haloperidol was not different from IM placebo on the PANSS-EC at 24 hours after the first injection, whereas all doses of IM olanzapine were. The response rates for IM olanzapine at 5.0 to 10 mg and IM haloperidol at 7.5 mg were more than double those of IM placebo and superior at 2 hours after the first IM injection. Overall, these efficacy results provide evidence of the superiority of IM olanzapine at 5.0, 7.5, and 10.0 mg and haloperidol at 7.5 mg compared with IM placebo in the treatment of acute agitation in schizophrenia. Furthermore, these data suggest that 10.0 mg of IM olanzapine may have efficacy advantages in comparison with 7.5 mg of IM haloperidol, as reflected by its more rapid onset of effect, the ABS and ACES results, and the persistence of effect at 24 hours.

Acute dystonia is frightening and distressing to patients and has been associated with noncompliance with medication.[42,43] Acute dystonia was spontaneously reported in 5.0% (2/40) of IM haloperidol-treated patients but in none of those treated with IM olanzapine or IM placebo. Furthermore, there was a lower incidence of treatment-emergent parkinsonism among IM olanzapine-treated patients than IM haloperidol-treated patients; in addition, numerically more patients treated with IM haloperidol than with IM olanzapine received anticholinergic medication. These findings are in keeping with previous comparisons of oral olanzapine vs oral haloperidol[44] and suggest that IM olanzapine may have safety advantages compared with IM haloperidol regarding extrapyramidal symptoms.

The incidence of the most frequently reported adverse event in patients treated with IM olanzapine (hypotension) was no different from that with IM placebo. Furthermore, there were no differences in the ECG QTc interval from the time of first injection until 2 or 24 hours later for any of the IM olanzapine treatment groups compared with IM haloperidol or IM placebo. This result is in accordance with findings from previous oral olanzapine studies[45-47] and suggests that the ECG safety of IM olanzapine is comparable with that of IM placebo. The ECG safety of IM haloperidol was further confirmed by this study.

Overall, these results suggest that IM olanzapine has a safety profile similar to that of oral olanzapine and may be superior in this regard to IM haloperidol. To address potential safety concerns regarding repeated IM olanzapine dosing, we conducted an open-label pharmacokinetics study of 3 consecutive doses of IM olanzapine at 10.0 mg given 4 hours apart within 24 hours.[32] These data demonstrated that olanzapine plasma concentrations were all within the range of steady-state plasma concentrations observed with a daily oral dose of olanzapine. Thus, if doses of 10 mg per injection of IM olanzapine are used, it seems prudent to recommend that the cumulative daily dose of olanzapine (including orally administered olanzapine) should not exceed 30 mg until further experience is gained with this formulation in the clinical setting.

In summary, this study provides evidence that 2.5, 5.0, 7.5, and 10.0 mg per injection of IM olanzapine exhibit a dose-response relationship in the treatment of acute agitation in patients with schizophrenia and demonstrate a favorable safety profile. A dose of 10.0 mg per injection of IM olanzapine is probably most effective for the majority of patients.

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