Efficacy and Safety of Intramuscular Aripiprazole in Patients With Acute Agitation: A Randomized, Double-Blind, Placebo-Controlled Trial

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Objective: This multicenter, randomized, double-blind, placebo-controlled study evaluated the efficacy and safety of intramuscular (IM) aripiprazole in patients with acute agitation with a DSM-IV diagnosis of schizophrenia, schizoaffective disorder, or schizophreniform disorder.

Method: Patients were randomly assigned to IM aripiprazole 1 mg, 5.25 mg, 9.75 mg, or 15 mg; IM haloperidol 7.5 mg; or placebo and observed for 24 hours. The primary efficacy measure was mean change in the Positive and Negative Syndrome Scale-Excited Component (PEC) score from baseline to 2 hours after initial dosing. Secondary measures included the Agitation-Calmness Evaluation Scale (ACES) score. The study was carried out at 50 centers worldwide between April 2002 and January 2003.

Results: A total of 357 patients were randomly assigned to treatment. Intramuscular aripiprazole 5.25 mg, 9.75 mg, and 15 mg and IM haloperidol 7.5 mg demonstrated significantly greater reduction in the primary efficacy measure versus placebo. These changes were statistically significant as early as 45 minutes for the IM aripiprazole 9.75-mg group, with a trend toward significance ($p = .051$) at 30 minutes. Intramuscular haloperidol 7.5 mg first showed a significant reduction in PEC score versus placebo at 105 minutes. At 30 minutes, significantly more patients responded (defined as a greater than or equal to 40% reduction in PEC score) to IM aripiprazole 9.75 mg versus placebo (27% vs. 13%, $p = .05$). Intramuscular aripiprazole 9.75 mg significantly improved agitation, without oversedation, as measured by change in ACES score from baseline to 2 hours versus placebo ($p = .003$). No patient discontinued the study because of treatment-emergent adverse events. Extrapyramidal symptoms occurred most frequently in the IM haloperidol group. The most common adverse event in IM aripiprazole recipients was headache.

Conclusion: Intramuscular aripiprazole 9.75 mg is a rapidly effective and well-tolerated alternative to IM haloperidol for the control of agitation, without oversedation, in patients with schizophrenia, schizoaffective disorder, or schizophreniform disorder.

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The majority of patients with schizophrenia, schizoaffective disorder, or schizophreniform disorder experience several acute episodes requiring hospitalization during the course of their illness, and approximately 20% of these patients need treatment for acute agitation.[1] Patients with acute agitation associated with schizophrenia are at risk of harm to themselves and others and require medication for rapid symptom control. Some patients may not be able to take oral drugs and, in these patients, it may be necessary to use an intramuscular (IM) form of medication.[2]

Intramuscular haloperidol is the standard IM antipsychotic medication used in the treatment of acute agitation. It is typically administered in the dose range of 5 to 10 mg

up to once every 2 hours. Conventional antipsychotics, however, are associated with acute extrapyramidal symptoms (EPS), such as dystonia, akathisia, and orthostatic hypotension, as well as side effects that can exacerbate the distress experienced by the patient. The early use of an effective agent with few side effects is known to improve overall adherence to therapy and facilitate the development of a solid therapeutic alliance, which translates into benefits for the long-term clinical outcome.[3]

Oral aripiprazole has demonstrated efficacy with good tolerability in patients with acute psychosis, but there remains a need for injectable formulations of atypical antipsychotics to control acutely agitated, hospitalized patients. Therefore, an IM formulation of aripiprazole was developed. The current randomized, double-blind study was carried out to investigate the efficacy and safety of IM aripiprazole (1 mg, 5.25 mg, 9.75 mg, or 15 mg) or IM haloperidol 7.5 mg versus placebo in the treatment of acute agitation in patients with schizophrenia, schizoaffective disorder, or schizophreniform disorder.

METHOD

Study Design

This dose-ranging, multicenter, randomized, double-blind, placebo-controlled study was carried out at 50 centers worldwide (30 in the United States and 20 others) between April 2002 and January 2003. Patients were eligible for inclusion in the study if they had symptoms of acute agitation and were diagnosed with schizophrenia, schizoaffective disorder, or schizophreniform disorder according to the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV) criteria.[4] Patients were required to have a baseline Positive and Negative Syndrome Scale (PANSS)-Excited Component (PEC) score greater than or equal to 15 and less than or equal to 32 and a score greater than or equal to 4 (moderate) on at least 2 of the 5 PEC items. All patients were at least 18 years old and were deemed by the treating clinician to be appropriate candidates for IM therapy for acute agitation. Prior to random assignment, patients were required to discontinue all other antipsychotic medication for the duration of the study and to provide informed consent. Patients were excluded from the study if they had psychoactive substance dependence within 2 months of the study start; required involuntary restraint; were suicidal; had a neurologic or psychiatric condition other than schizophrenia, schizoaffective disorder, or schizophreniform disorder; had a significant medical condition; or were known nonresponders to antipsychotic medication.

The study was conducted in compliance with Good Clinical Practice and with approval from the relevant institutional review board or independent ethics committee at each center. Patients or their legally authorized representatives gave written informed consent before any protocol-required procedures were performed.

Efficacy Outcome Measures and Assessment Scales

This study tested the primary hypothesis that at least 1 of the IM aripiprazole study doses would result in a greater mean change from baseline to 2 hours in PEC score than placebo postinitial dose. The PEC scale consists of 5 items of the PANSS.[5] These items are excitement (item P4), hostility (P7), tension (G4), uncooperativeness (G8), and poor impulse control (G14). Each item is scored on a scale of 1 (absent) to 7 (extreme). Improvement is represented by a reduction in the score. Response was defined as a reduction greater than or equal to 40% in PEC score from baseline to 2 hours.

Other rating scales used to measure secondary outcomes included the Agitation-Calmness Evaluation Scale (ACES),[6] the Corrigan Agitated Behavior Scale (CABS),[7] the Clinical Global Impressions-Severity of Illness scale (CGI-S),[8] the Clinical Global Impressions-Improvement scale (CGI-I),[8] and the Total and Positive subscales of the Brief Psychiatric Rating Scale (BPRS).[9]

All efficacy evaluations were performed at baseline and every 15 minutes for the first 2 hours; at 4, 6, 12, and 24 hours after the initial dose; and just before each repeat dose of study medication or rescue medication, if administered. Efficacy evaluations for any repeat dose of medication given were also performed at 1 and 2 hours after that dose.

Treatment

Patients were randomly assigned in a 1:1:1:1:1:1 ratio to the 6 study arms. An initial dose of IM study medication was administered by injection within 1 hour of the baseline assessment. Patients were randomly assigned to an initial dose of IM aripiprazole 1 mg (0.5 mL of a 2 mg/mL solution), 5.25 mg (0.7 mL of a 7.5 mg/mL solution to approximate a dose of 5 mg), 9.75 mg (1.3 mL of a 7.5 mg/mL solution to approximate a dose of 10 mg), or 15 mg (2.0 mL of a 7.5 mg/mL solution); IM haloperidol 7.5 mg (1.5 mL of a 5 mg/mL solution); or IM placebo. Intramuscular haloperidol was used as an active control. Patients were permitted to receive up to 3 doses of study drug or placebo within the first 20 hours; a second dose was given, if needed, at least 2 hours after the initial dose, followed by a third dose, if needed, at least 2 hours after the second dose and no later than 20 hours after the initial dose. For patients randomly assigned to placebo, the first and second doses contained placebo and the third dose contained 15 mg IM aripiprazole. The study permitted lorazepam (or benzodiazepine equivalent) to be used as rescue medication but not until at least 60 minutes after the second dose if the PEC score was unchanged or worsened from the baseline value or if the investigator deemed it absolutely necessary; no other psychotropic drugs were

permitted during the treatment and observation periods. Study drugs were not administered after rescue medication was given.

Dose selection for this study was based on the clinical experience from a phase 1 study in healthy volunteers (Data on file, Bristol-Myers Squibb Co., Princeton, N.J.), in which subjects received doses of 1 mg, 3 mg, 7.5 mg, 15 mg, or 30 mg of IM aripiprazole or 5 mg or 7.5 mg of IM haloperidol.

Because the study drugs had different dilution instructions, no blinding was used during the preparation of injections. In most cases, the same person prepared and administered the drug. To prevent the occurrence of bias in the efficacy and EPS evaluations, study investigators conducting the assessments were blinded to treatment. In the case of 1 medical emergency, the treating physician broke the blind design, as knowledge of the investigational product was considered to be critical to the patient's management, but the assessor remained blinded.

Safety Outcome Measures

Safety assessments included continuous assessment and spontaneous reporting of any adverse events (AEs) and further assessment of EPS using the Simpson-Angus Scale (Simpson-Angus)[10] and the Barnes Akathisia Rating Scale (BARNES)[11] at baseline and at 2, 4, 6, 12, and 24 hours after administration of the initial dose of study drug. Adverse events were classified according to version 7 of the *Medical Dictionary for Regulatory Activities* (MedDRA).[12] Treatment-emergent AEs were defined as those identified by investigators to be "certainly," "probably," or "possibly" related to the study drug. The change from baseline in Simpson-Angus and BARNES scores were analyzed using analysis of covariance (ANCOVA).

Clinical laboratory tests (hematology, serum chemistry, and urinalysis) were performed at baseline and at 6 and 24 hours after administration of the initial dose of study drug. Vital signs were checked at baseline and at frequent intervals throughout the study period. The presence of cardiac abnormalities was assessed by 12-lead electrocardiogram (ECG) at screening and throughout the study period. For the evaluation of QT interval, a potentially clinically significant increase was defined as an on-treatment value greater than 450 ms. Corrected QT interval (QTc) was calculated using Bazett's formula ($QTc_B = QT/RR^{0.5}$), the U.S. Food and Drug Administration (FDA) Neuropharmacological Division formula ($QTc_N = QT/RR^{0.37}$), and the Fridericia correction formula ($QTc_F = QT/RR^{0.33}$).

Safety data analyses were carried out on all patients who were randomly assigned to treatment and who had received at least 1 dose of study drug. In patients randomly assigned to placebo, safety evaluations occurring after a third injection (which was IM aripiprazole 15 mg) were not included in the safety data analyses but were considered separately.

Statistical Methods

A sample size was calculated to yield 90% power to differentiate between placebo and at least 1 of the 3 higher-dose IM aripiprazole groups using the threshold of mean change from baseline in PEC scores of 4.0. From this calculation, a minimum of 324 randomly assigned patients was estimated to be required to obtain 306 evaluable patients (51 per treatment group). This estimate assumed a standard deviation of 5.4 and a 2-sided test at the 0.0167 level of significance (adjusted for 3 comparisons vs. placebo to ensure an overall significance level of less than .05 overall).

Efficacy analyses were carried out on all patients who were randomly assigned to treatment, had received at least 1 dose of study drug, and had at least 1 postbaseline efficacy evaluation. Allowances for discontinuations and missing data were made using the last-observation-carried-forward (LOCF) approach. Observed-case (OC) analyses were also performed for confirmatory purposes.

Baseline comparisons were made using the analysis-of-variance (ANOVA) model, adjusting for treatment and country. Between-group differences (active treatment vs. placebo) in change from baseline scores were made using the ANCOVA model with baseline score as the covariate and adjusting for treatment and country. Treatment differences versus placebo were calculated as least squares (LS) means with 95% confidence intervals (CIs), and the significance was calculated using pairwise comparisons based on the ANOVA/ANCOVA models. Primary efficacy analyses were adjusted for multiple comparisons.

The significance of response differences between treatments was evaluated using the Cochran-Mantel-Haenszel (CMH) general association test. Significance values of treatment differences for CGI-I scores were generated by the CMH row means test.

Estimated time to response was determined using Kaplan-Meier survival analysis curves. The log-rank test was used to determine significance values for differences between curves. Relative risk (RR) estimates for likelihood of response versus placebo were calculated using the Cox proportional hazards regression model, controlling for treatment. P values equal to or less than .05 were considered statistically significant.

RESULTS

Patient Disposition

Of the 357 patients randomly assigned to treatment, 338 (95%) completed the study. The reasons for discontinuation were withdrawal of consent in 12 patients (3%), AEs in 2 patients (less than 1%; 1 patient in each of the IM aripiprazole 9.75-mg and 15-mg groups), lack of efficacy in 1 patient in the placebo group (less than 1%), and other known cause in 4 patients (1%; 1 each in the

Table 1. Patient Demographics and Baseline Characteristics

Variable	Placebo (N = 62)	Intramuscular Aripiprazole 1 mg (N = 57)	Intramuscular Aripiprazole 5.25 mg (N = 63)	Intramuscular Aripiprazole 9.75 mg (N = 57)	Intramuscular Aripiprazole 15 mg (N = 58)	Intramuscular Haloperidol, 7.5 mg (N = 60)
Age, mean (SD)	40.29 (10.74)	41.46 (10.12)	39.46 (10.19)	41.18 (10.88)	44.24 (9.96)	40.85 (10.16)
(range), y	(19–62)	(20–64)	(21–63)	(21–64)	(20–66)	(18–64)
Men, N (%)	32 (52)	37 (65)	35 (56)	36 (63)	35 (60)	39 (65)
Women, N (%)	30 (48)	20 (35)	28 (44)	21 (37)	23 (40)	21 (35)
Race, N (%)						
White	38 (61)	39 (68)	47 (75)	41 (72)	40 (69)	43 (72)
Black	17 (27)	12 (21)	12 (19)	9 (16)	13 (22)	13 (22)
Asian/Pacific Islander	0 (0)	0 (0)	1 (2)	2 (4)	0 (0)	0 (0)
Hispanic/Latino	7 (11)	5 (9)	2 (3)	5 (9)	4 (7)	3 (5)
American/Alaskan native	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)
Other	0 (0)	0 (0)	1 (2)	0 (0)	1 (2)	0 (0)
Underlying diagnosis, N (%)						
Schizophrenia	39 (63)	30 (53)	41 (65)	37 (65)	44 (76)	46 (77)
Schizoaffective disorder	21 (34)	26 (46)	21 (33)	18 (32)	14 (24)	13 (22)
Schizophreniform disorder	2 (3)	1 (2)	1 (2)	2 (4)	0 (0)	1 (2)

placebo and IM aripiprazole 5.25-mg groups and 2 in the IM haloperidol group).

Patient Demographics and Baseline Characteristics

In total, 378 patients were screened and, of these, 357 were randomly assigned to double-blind treatment: IM aripiprazole 1 mg (N = 57), IM aripiprazole 5.25 mg (N = 63), IM aripiprazole 9.75 mg (N = 57), IM aripiprazole 15 mg (N = 58), IM haloperidol 7.5 mg (N = 60), and placebo (N = 62). The demographic characteristics and underlying diagnoses of treatment groups were similar (Table 1). Two thirds of the patients (66%) had a diagnosis of schizophrenia.

Efficacy

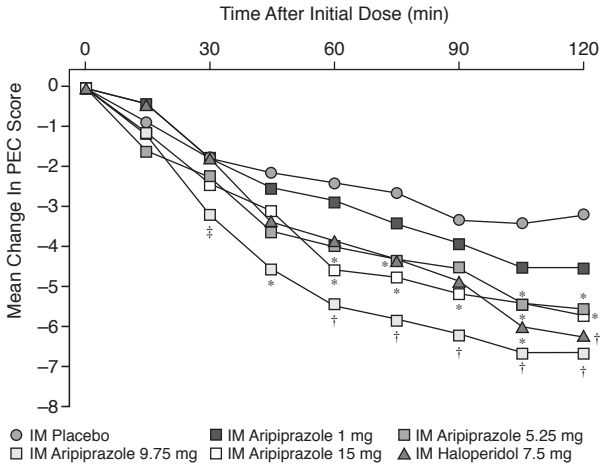
Significantly greater reductions in PEC scores were observed at 2 hours with all doses of IM aripiprazole (except the 1-mg dose) and IM haloperidol 7.5 mg compared with placebo ($p < .01$ for all 4 comparisons with placebo; Figure 1). These changes were statistically significant as early as 45 minutes for the IM aripiprazole 9.75-mg group, with a trend toward significance ($p = .051$) at 30 minutes (Figure 1). A significant difference between IM haloperidol and placebo was first seen at 105 minutes ($p = .004$). Mean changes in PEC scores were comparable for male and female patients.

There were significantly greater mean changes from baseline in ACES scores at 2 hours postinitial dose with IM aripiprazole 9.75 mg and IM haloperidol 7.5 mg compared with placebo (both $p \leq .01$). Results for the key secondary efficacy measures are summarized in Table 2.

The 5.25-mg to 15-mg doses of IM aripiprazole and IM haloperidol demonstrated a significant decrease from baseline in CABS score versus placebo at 2 hours ($p = .007$ for IM aripiprazole 5.25 mg; $p < .001$ for IM aripiprazole 9.75 mg and 15 mg and IM haloperidol; Table 2). There was a trend toward significance for IM aripiprazole 1 mg ($p = .054$ vs. placebo; Table 2).

The PEC-defined response rate at 60 and 120 minutes postinitial dose was greater with IM aripiprazole 9.75 mg compared with placebo ($p < .02$ and $p < .04$, respectively). The response rate with IM aripiprazole 15 mg was significantly greater than with placebo at the 60-minute observation ($p = .041$), and there was a trend toward significance ($p = .053$) at 120 minutes (Figure 2). The re-

Figure 1. Time Course of Mean Change in PEC Score From Baseline at 0 Hours to 2 Hours Postinitial Dose[a,b]



[a]Mean baseline PEC score: IM placebo = 19.21, IM aripiprazole 1 mg = 19.16, IM aripiprazole 5.25 mg = 19.46, IM aripiprazole 9.75 mg = 19.44, IM aripiprazole 15 mg = 19.34, IM haloperidol = 18.89.
[b]Analysis-of-covariance model, controlling for treatment, country, and baseline value, was used for mean change from baseline comparisons.
*$.001 < p \leq .05$ vs. placebo.
†$p \leq .001$ vs. placebo.
‡$p = .051$ vs. placebo.
Abbreviations: IM = intramuscular, PEC = Positive and Negative Syndrome Scale-Excited Component.

Table 2. Key Secondary Efficacy Results at 2 Hours Postinitial Dose: Mean Change in ACES, CABS, CGI-S, BPRS Total and Positive, and CGI-I Scores at 2 Hours and PEC-Defined Response Rate at 2 Hours (last observation carried forward)

		Intramuscular Aripiprazole				Intramuscular Haloperidol,
Variable	Placebo (N = 61)	1 mg (N = 56)	5.25 mg (N = 62)	9.75 mg (N = 56)	15 mg (N = 58)	7.5 mg (N = 57)
ACES score, mean (95% CI)						
Baseline	2.07 (1.95 to 2.19)	2.09 (1.96 to 2.21)	2.14 (2.02 to 2.25)	2.11 (1.98 to 2.23)	2.08 (1.95 to 2.20)	2.07 (1.95 to 2.19)
Change at 2 h	0.66 (0.23 to 1.08)	0.65 (0.22 to 1.08)	1.01 (0.60 to 1.42)	1.50** (1.06 to 1.94)	0.99 (0.55 to 1.44)	1.50** (1.06 to 1.94)
CABS score, mean (95% CI)						
Baseline	31.18 (29.44 to 32.91)	31.45 (29.68 to 33.23)	30.05 (28.36 to 31.74)	31.51 (29.71 to 33.31)	31.22 (29.42 to 33.02)	32.10 (30.31 to 33.89)
Change at 2 h	–2.95 (–4.69 to –1.21)	–5.16 (–6.94 to –3.38)	–5.97** (–7.66 to –4.27)	–7.08*** (–8.89 to –5.28)	–7.04*** (–8.85 to –5.24)	–8.13*** (–9.93 to –6.33)
CGI-S score, mean (95% CI)						
Baseline	4.91 (4.70 to 5.11)	4.85 (4.64 to 5.06)	4.81 (4.61 to 5.01)	5.10 (4.89 to 5.32)	4.89 (4.67 to 5.10)	4.97 (4.76 to 5.19)
Change at 2 h	–0.42 (–0.71 to –0.13)	–0.63 (–0.93 to –0.33)	–0.82* (–1.10 to –0.54)	–1.08*** (–1.38 to –0.77)	–0.99** (–1.29 to –0.69)	–0.91* (–1.21 to –0.61)
CGI-I score at 2 h, mean (SE)	3.46 (0.11)	3.07* (0.13)	2.82*** (0.14)	2.64*** (0.17)	2.66*** (0.14)	2.72*** (0.15)
PEC response rate[a] at 2 h, N (%)	22 (36)	21 (38)	31 (50)	30* (54)	32 (55)	34* (60)
BPRS total score, mean (95% CI)						
N	58	55	61	52	56	50
Baseline	58.29 (55.23 to 61.35)	57.79 (54.69 to 60.89)	57.03 (54.08 to 59.98)	58.66 (55.46 to 61.87)	58.16 (54.99 to 61.32)	58.93 (55.69 to 62.16)
Change at 2 h	–4.80 (–7.31 to –2.29)	–6.53 (–9.07 to –3.99)	–8.16* (–10.58 to –5.73)	–8.19* (–10.82 to –5.56)	–8.88* (–11.47 to –6.29)	–10.22*** (–12.87 to –7.57)
BPRS positive score, mean (95% CI)						
N	58	55	61	52	57	51
Baseline	15.90 (14.85 to 16.95)	15.65 (14.59 to 16.71)	16.01 (15.00 to 17.02)	16.44 (15.34 to 17.54)	15.96 (14.88 to 17.04)	16.40 (15.29 to 17.50)
Change at 2 h	–0.99 (–1.70 to –0.28)	–1.20 (–1.92 to –0.48)	–1.47 (–2.15 to –0.79)	–1.61 (–2.35 to –0.86)	–1.86 (–2.59 to –1.13)	–1.84 (–2.58 to –1.09)

[a]The response rate was defined as the proportion of patients with ≥ 40% reduction in PEC score from baseline.
*.01 < p value ≤ .05 vs. placebo.
**.001 < p value ≤ .01 vs. placebo.
***p value ≤ .001 vs. placebo.
Abbreviations: ACES = Agitation-Calmness Evaluation Scale, BPRS = Brief Psychiatric Rating Scale, CABS = Corrigan Agitated Behavior Scale, CGI-I = Clinical Global Impressions-Improvement scale, CGI-S = Clinical Global Impressions-Severity of Illness scale, PEC = Positive and Negative Syndrome Scale-Excited Component.

sponse rate with IM haloperidol was also significant at 120 minutes ($p < .02$ vs. placebo), but not at 60 minutes.

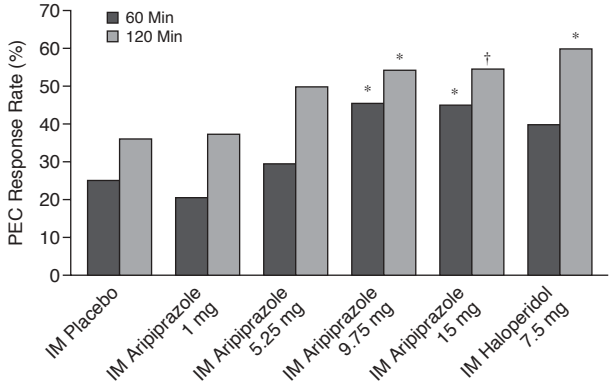
At 2 hours postinitial dose (LOCF), the CGI-I scores showed that IM aripiprazole 5.25 mg, 9.75 mg, and 15 mg and IM haloperidol 7.5 mg were significantly more effective than placebo (all $p < .001$; Table 2). Intramuscular aripiprazole 1 mg was also significantly more effective than placebo ($p < .02$). Statistically significant improvement was demonstrated as early as 30 minutes postinitial dose with IM aripiprazole 9.75 mg ($p < .03$) and at 45 minutes with IM haloperidol ($p < .02$) (Figure 3), and there was a trend toward significance at 15 minutes with IM aripiprazole 9.75 mg ($p = .056$).

The IM aripiprazole 5.25-mg, 9.75-mg, and 15-mg and IM haloperidol 7.5-mg groups demonstrated significantly greater mean changes from baseline in CGI-S scores (LOCF) compared with placebo at 2 hours (all $p < .05$; Table 2). Intramuscular aripiprazole 9.75 mg demonstrated significantly greater CGI-S improvement by 30 minutes ($p < .02$), and this was maintained at each timepoint up to 2 hours. Intramuscular haloperidol 7.5 mg showed significant efficacy, as determined by CGI-S, at 45 minutes ($p < .05$) and then not until 90 minutes ($p < .05$), and then it was maintained up to 2 hours.

Mean changes from baseline to 2 hours for BPRS total score were significantly greater than placebo with IM aripiprazole 5.25 mg ($p = .037$), 9.75 mg ($p = .043$), and 15 mg ($p = .013$) and IM haloperidol 7.5 mg ($p = .001$). Mean changes in BPRS positive scores from baseline to 2 hours were not significantly different from placebo in any active treatment group (Table 2).

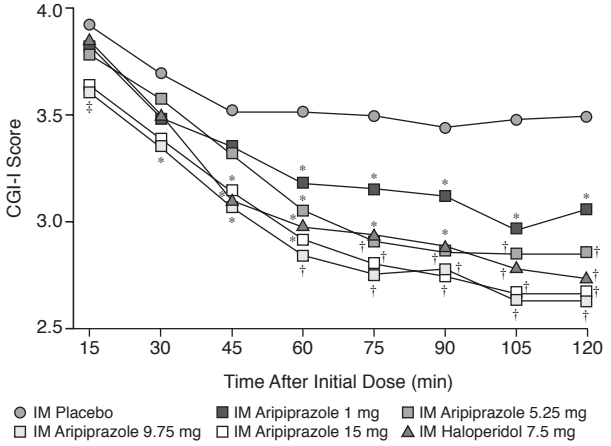
Patients in the placebo group required significantly more injections than those in the IM haloperidol group and the IM aripiprazole 5.25-mg to 15-mg groups ($p < .05$ for all comparisons). Seventy-four percent of IM haloperidol-treated patients (42/57) received 1 injection, 19% (11/57) received 2 injections, and 7% (4/57) received 3 injections. In the IM aripiprazole 5.25-mg, 9.75-mg, and 15-mg groups, 56% to 60% of patients received 1 injection, 19% to 31% received 2 injec-

Figure 2. Response Rate[a] at 60 Minutes and 120 Minutes (last observation carried forward)



[a]Response rate was defined as the proportion of patients with a PEC score reduction ≥ 40% from baseline. Cochran-Mantel-Haenszel general association test, controlling for treatment and country, was used for pairwise comparisons.
*p ≤ .05 vs. placebo.
†p = .053 vs. placebo.
Abbreviations: IM = intramuscular, PEC = Positive and Negative Syndrome Scale-Excited Component.

Figure 3. Time Course of Mean CGI-I Score at 15 Minutes to 2 Hours Postinitial Dose[a]



[a]Cochran-Mantel-Haenszel row means score test, controlling for treatment and country, was used for pairwise comparisons.
*.001 < p ≤ .05 vs. placebo.
†p ≤ .001 vs. placebo.
‡p = .056 vs. placebo.
Abbreviations: CGI-I = Clinical Global Impressions-Improvement scale, IM = intramuscular.

Table 3. Proportion of Patients Reporting at Least 1 Treatment-Emergent Adverse Event (AE) and the Incidence of Treatment-Emergent AEs Reported in at Least 5% of Patients in Any Study Group

Variable	Placebo (N = 61)[a]	Intramuscular Aripiprazole				Intramuscular Haloperidol, 7.5 mg (N = 57)
		1 mg (N = 56)	5.25 mg (N = 62)	9.75 mg (N = 56)	15 mg (N = 58)	
Patients reporting at least 1 adverse event, N (%)	18 (29.5)	28 (50.0)	30 (48.4)	25 (44.6)	27 (46.6)	28 (49.1)
Cardiac disorders, N (%)						
Tachycardia	1 (1.6)	3 (5.4)	2 (3.2)	4 (7.1)	0 (0)	1 (1.8)
Sinus tachycardia	1 (1.6)	1 (1.8)	0 (0)	0 (0)	0 (0)	3 (5.3)
Gastrointestinal disorders, N (%)						
Vomiting	1 (1.6)	1 (1.8)	0 (0)	2 (3.6)	3 (5.2)	1 (1.8)
Nausea	2 (3.3)	0 (0)	6 (9.7)	6 (10.7)	2 (3.4)	1 (1.8)
Nervous system disorders, N (%)						
Dizziness	4 (6.6)	4 (7.1)	7 (11.3)	4 (7.1)	7 (12.1)	4 (7.0)
Headache	1 (1.6)	4 (7.1)	11 (17.7)	6 (10.7)	8 (13.8)	2 (3.5)
Somnolence	3 (4.9)	3 (5.4)	5 (8.1)	3 (5.4)	6 (10.3)	7 (12.3)
Akathisia	0 (0)	0 (0)	2 (3.2)	3 (5.4)	0 (0)	6 (10.5)
Dystonia	0 (0)	0 (0)	0 (0)	1 (1.8)	1 (1.7)	4 (7.0)
Psychiatric disorders, N (%)						
Agitation	1 (1.6)	0 (0)	0 (0)	2 (3.6)	3 (5.2)	1 (1.8)

[a]Incidence of AEs in the placebo group excludes events with onset after the third intramuscular injection (intramuscular aripiprazole 15 mg).

tions, and 9% to 24% required 3 injections. By comparison, the majority of placebo recipients required 2 or more injections (18% [11/61] received 2 and 44% [27/61] received 3). Twenty-one percent of placebo-treated patients (13/61) received rescue medication compared with 20% (11/56) in the IM aripiprazole 1-mg group and 8% (5/62), 13% (7/56), and 21% (12/58) of those in the IM aripiprazole 5.25-mg, 9.75-mg, and 15-mg groups, respectively. Eleven percent of IM haloperidol recipients (6/57) required rescue medication.

Safety Data

In total, 350 patients were included in the safety analysis. Of these, 156 (44.6%) reported at least 1 AE during the study (Table 3). Two patients discontinued because of an AE: 1 in the IM aripiprazole 9.75-mg group and 1 in the IM aripiprazole 15-mg group. Neither event was considered likely to be related to the study drug.

Table 3 shows the incidence of treatment-emergent AEs reported by greater than or equal to 5% of patients in any treatment group. Of these, the most commonly reported AEs were headache (13%), dizziness (10%), som-

nolence (7%), and nausea (6%) in the IM aripiprazole groups and somnolence (12%), akathisia (11%), dystonia (7%), and dizziness (7%) in the IM haloperidol group. The number of patients reporting injection site pain was low and was higher in the placebo group than in the active treatment groups: 2 patients (3%) in the placebo group and 1 patient (2%) in each of the IM aripiprazole 5.25-mg, 9.75-mg, and 15-mg groups.

Serious AEs were reported by 7 patients: 1 (2%) in the placebo group, 1 (2%) in the IM aripiprazole 1-mg group, 2 (3%) in the IM aripiprazole 5.25-mg group, and 3 (5%) in the IM aripiprazole 9.75-mg group. None of the AEs were considered to be related to the study drug. No deaths were reported during the study. In the 1 patient for whom the blinding was broken, a serious AE of severe tonic-clonic seizure was experienced. This patient was assigned to the IM aripiprazole 9.75-mg group; however, the investigator considered that this AE was not likely to be related to the study medication.

The incidence of laboratory abnormalities was similar across all study groups, no dose-response relationships were noted, and there were no clinical concerns regarding any laboratory abnormalities or ECG measurements. The incidence of QTc abnormalities that was observed with the standard 12-lead ECG was higher for QTc_B in the IM haloperidol group (6.5%; 3/46) and in the IM aripiprazole 1-mg (7.8%; 4/51), 5.25-mg (6.8%; 4/59), and 15-mg (6.0%; 3/50) groups than in the placebo group (2.4%; 1/41); however, when the QTc_N and QTc_F formulas were used, there were no noteworthy treatment differences versus placebo. When ambulatory 12-lead ECGs were analyzed, there were no notable differences in QTc across treatment groups using any formulas.

EPS-Related AEs and EPS Rating Scale Data

Overall, the incidence of EPS-related AEs was higher in the active treatment groups compared with placebo. As shown in Table 3, akathisia occurred in 11% of IM haloperidol recipients and 2% (0%–5%) of IM aripiprazole-treated patients. Similarly, dystonia occurred in more IM haloperidol than IM aripiprazole recipients (7% vs. 0%–2%, respectively). No cases of akathisia or dystonia were observed in the placebo group. No patients discontinued from the study because of EPS-related AEs.

The mean changes in Simpson-Angus total scores from baseline were not significantly different from those of placebo at any dose level or timepoint during the study, except at 24 hours, when a significantly lower decrease in Simpson-Angus total scores with IM haloperidol (less reduction in EPS) was seen versus placebo for the OC analyses only ($p = .012$), and at 12 hours, when there was a significant difference between 1 mg versus placebo ($p = .038$). A similar pattern was observed when between-group differences in BARNES scores were compared. There were no significant differences between the active treatment groups and placebo, except for the OC analyses on 3 occasions. Intramuscular aripiprazole 15 mg was associated with significantly improved akathisia at the 4-hour measurement, as indicated by a more pronounced reduction in BARNES score compared with placebo ($p = .041$; OC). The other significant differences were observed at the 24-hour assessment, when IM haloperidol 7.5 mg and aripiprazole 9.75 mg were associated with more limited improvement in akathisia (i.e., a lower reduction in BARNES score) than placebo ($p = .012$ and $p = .031$, respectively; OC).

DISCUSSION

Patients with acute agitation associated with schizophrenia are potentially at risk of harm to themselves or others. Whereas it is imperative to ameliorate the patients' symptoms as soon as possible, consideration must also be given to the impact that acute treatment may have on future management. Treating a highly distressed patient with an agent that leads to further anguish may result in decreased compliance or refusal to take medication during the maintenance phase of treatment.

The management of acute agitation has traditionally used benzodiazepines (e.g., lorazepam), but problems with excessive sedation or "oversedation" have led to the increased use of IM antipsychotics in place of, or in combination with, benzodiazepines. Although initial calming effects might be regarded as useful, oversedation is not desirable, as it may interfere with ongoing patient evaluation and treatment participation.[13] Conventional antipsychotics, used because they are available in IM formulation, are associated with a high propensity for causing acute EPS. Such symptoms can be particularly problematic in patients who require several days of IM therapy to gain sufficient control of their symptoms before transferring to oral therapy. Further difficulties, such as breakthrough symptoms,[14] may then be introduced by the need to transfer some patients from conventional antipsychotics to oral atypical agents.

Atypical antipsychotics are now the clearly preferred treatment for patients with schizophrenia, with this class comprising more than 70% of antipsychotic prescriptions in the United States.[15] However, their use in acute psychosis and agitation has been limited until recently by the lack of IM formulations. Recently, increasing clinical data concerning the use of IM atypical antipsychotics in patients with acute agitation are becoming available. In the current study, IM aripiprazole was found to be efficacious in this patient population at doses of 5.25 mg to 15 mg, but as the 9.75-mg dose is most likely to be recommended for further study, it will be used as the basis for this discussion.

Intramuscular aripiprazole 9.75 mg was as effective as IM haloperidol 7.5 mg, providing rapid and significant improvement for patients with acute agitation associated

with schizophrenia, as seen by reduction of the PEC score. Although caution should be taken when comparing data across studies, these findings appear to be similar to those achieved with IM olanzapine in patients with acute agitation associated with schizophrenia.[16,17] As with IM aripiprazole in this study, the improvements observed with IM olanzapine were significantly better than those achieved with placebo and comparable to those achieved with IM haloperidol 7.5 mg. At 24 hours postdose, the mean change in PEC score with IM olanzapine was similar to the 7.9-point reduction achieved with IM aripiprazole 9.75 mg at 24 hours in the current study.

Secondary investigations undertaken in this study support the hypothesis that the antipsychotic efficacy of IM atypical antipsychotics is the result of an intrinsic calming effect rather than an artifact of excessive sedation. Intramuscular aripiprazole 9.75 mg improved the baseline ACES score by a mean of 1.5 points by the 2-hour postadministration timepoint, enough to represent significantly improved agitation, but not enough to cause excessive sedation (scores of 8 or 9 corresponding to "deep sleep"[8] or "unarousable"[9]). In this study and in the IM olanzapine trials, comparable results were reinforced by significant reductions in CABS scores, indicating amelioration of agitation.

Although studies of IM ziprasidone have also been performed in acutely agitated psychotic patients, the use of a different assessment scale, the Behavioral Activity Rating Scale, in these studies precludes direct comparison with the results discussed above.[18] Both IM olanzapine and IM ziprasidone are FDA-approved for the treatment of acute agitation in patients with schizophrenia.

Other tolerability assessments further indicated that IM aripiprazole is well-tolerated during acute administration. More than 90% of the AEs reported were of mild or moderate severity only, and there was no evidence that the incidence of treatment-emergent events increased with increasing IM aripiprazole dose. No patient discontinued the study at any dose for reasons considered likely to be related to the study drug. There were also no occurrences of treatment-emergent serious AEs or deaths in any treatment group, and there was no evidence of clinically significant laboratory or ECG abnormalities or QTc interval prolongation.

Overall, patients in the placebo group required significantly more injections than those in the IM haloperidol group or in any IM aripiprazole group. Placebo recipients also required the use of more rescue medication versus patients treated with IM aripiprazole 5.25 mg or 9.75 mg. The use of rescue medication in the IM aripiprazole 15-mg group was comparable to the placebo group and higher than with IM aripiprazole 5.25 mg or 9.75 mg. The variability in the use of rescue medication between the different IM aripiprazole groups is of note; however, meaningful clinical interpretation is difficult, owing to the relatively limited sample size of each group. These differences are likely attributable to variability observed within clinical studies.

In those placebo-treated patients who received a third injection, that third injection was IM aripiprazole 15 mg, which yielded a significant mean reduction in PEC score by 7 points compared with the evaluation prior to the third injection, providing uncontrolled additional evidence of efficacy.

The main limitation regarding the ability to generalize from these study data is that, although the patients enrolled were agitated to a degree that necessitated IM therapy, the study inclusion criteria required the enrolled patients to provide informed consent. Thus, these patients were not so severely agitated as to preclude provision of informed consent.

It is recommended that atypical antipsychotics should be used over typical antipsychotics whenever possible because of their advantages in treating the positive symptoms of psychosis and hostility that often drive hospitalization.[19] The introduction of IM formulations of atypical agents should provide those treating acutely psychotic patients with options that are more flexible and efficacious with improved safety profiles over typical agents. In this study, IM aripiprazole showed superior efficacy over placebo in the treatment of acute agitation in patients with schizophrenia, schizoaffective disorder, or schizophreniform disorder. In particular, IM aripiprazole 9.75 mg already showed a trend toward significantly greater reduction in PEC scores from baseline versus placebo at 30 minutes and was significantly effective earlier than any other dose and earlier than IM haloperidol. Intramuscular aripiprazole 9.75 mg also showed superiority over placebo in the key secondary measures (ACES, CABS, CGI-S, CGI-I) and showed similar efficacy to IM haloperidol. A favorable safety profile was demonstrated for all doses of IM aripiprazole studied, particularly with regard to lower rates of EPS compared with IM haloperidol, and the absence of any treatment-emergent serious AEs or discontinuations related to the study drug. As a result of these findings, IM aripiprazole 9.75 mg is recommended for further study in the treatment of acute agitation.

Drug names: aripiprazole (Abilify), haloperidol (Haldol and others), lorazepam (Ativan and others), olanzapine (Zyprexa), ziprasidone (Geodon).

REFERENCES

1. Pilowsky LS, Ring H, Shine PJ, et al. Rapid tranquillisation: a survey of emergency prescribing in a general psychiatric hospital. Br J Psychiatry 1992;160:831–835
2. Citrome L. Atypical antipsychotics for acute agitation: new intramuscular options offer advantages. Postgrad Med 2002;112:85–96
3. Perkins DO. Predictors of noncompliance in patients with schizophrenia. J Clin Psychiatry 2002;63:1121–1128
4. American Psychiatric Association. Diagnostic and Statistical Manual

of Mental Disorders, Fourth Edition. Washington, DC: American Psychiatric Association; 1994
5. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr Bull 1987;13:261–276
6. Meehan KM, Wang H, David SR, et al. Comparison of rapidly acting intramuscular olanzapine, lorazepam, and placebo: a double-blind, randomized study in acutely agitated patients with dementia. Neuropsychopharmacology 2002;26:494–504
7. Corrigan JD, Bogner JA. Factor structure of the Agitated Behavior Scale. J Clin Exp Neuropsychol 1994;16:386–392
8. Guy W. Assessment Manual for Psychopharmacology, US Department of Health, Education, and Welfare publication (ADM) 76-338, Rockville, Md: National Institute for Mental Health; 1976
9. Overall JE, Gorham DR. The Brief Psychiatric Rating Scale. Psychol Rep 1962;10:799–812
10. Simpson GM, Angus JW. A rating scale for extrapyramidal side effects. Acta Psychiatr Scand Suppl 1970;212:11–19
11. Barnes TR. A rating scale for drug-induced akathisia. Br J Psychiatry 1989;154:672–676
12. MedDRA: The Medical Dictionary for Regulatory Activities. Available at: http://www.meddramsso.com/mssoweb/index.htm. Accessed Dec 8, 2005
13. Battaglia J, Lindborg SR, Alaka K, et al. Calming versus sedative effects of intramuscular olanzapine in agitated patients. Am J Emerg Med 2003; 21:192–198
14. Weiden PJ, Aquila R, Dalheim L, et al. Switching antipsychotic medications. J Clin Psychiatry 1997;58(suppl 10):63–72
15. IMS Health. Atypical antipsychotics: generating evidence to inform policy and practice. Available at: http://research.imshealth.com/research/research_schizophrenia.htm. Accessed Dec 8, 2005
16. Breier A, Meehan K, Birkett M, et al. A double-blind, placebo-controlled dose-response comparison of intramuscular olanzapine and haloperidol in the treatment of acute agitation in schizophrenia. Arch Gen Psychiatry 2002;59:441–448
17. Wright P, Birkett M, David SR, et al. Double-blind, placebo-controlled comparison of intramuscular olanzapine and intramuscular haloperidol in the treatment of acute agitation in schizophrenia. Am J Psychiatry 2001;158:1149–1151
18. Zimbroff DL, Allen MH, Battaglia J, et al. Best clinical practice with ziprasidone IM: update after 2 years of experience. CNS Spectrums 2005;9(suppl 11):1–15
19. Currier GW, Trenton A. Pharmacological treatment of psychotic agitation. CNS Drugs 2002;16:219–228