Risperidone Liquid Concentrate and Oral Lorazepam Versus Intramuscular Haloperidol and Intramuscular Lorazepam for Treatment of Psychotic Agitation

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Background: Although agitation associated with psychosis is a common presentation in the psychiatric emergency service, there is no consensus concerning the best treatment. Standard treatment often consists of intramuscular (i.m.) injection of high-potency neuroleptics, sometimes combined with benzodiazepines. The objective of this study was to determine the relative efficacy, safety, and tolerability of oral risperidone versus intramuscular haloperidol, both in combination with lorazepam, for the emergency treatment of psychotic agitation in patients who are able to accept oral medications.

Method: A convenience sample of psychotic patients admitted to a large psychiatric emergency service who required emergency medication for the control of agitation and/or violence was offered risperidone (2 mg liquid concentrate) and oral lorazepam (2 mg) as an alternative to standard care at the institution, haloperidol (5 mg i.m.) and lorazepam (2 mg i.m.). Subjects who refused the oral medications were given the intramuscular treatment as a component of routine care.

Results: Thirty patients were enrolled in each treatment group. Although men were significantly more likely to choose oral medication ($\chi^2 = 5.165$, $p < .023$), other demographic characteristics did not differ significantly between the 2 treatment groups. Both groups showed similar improvement in agitation as measured by 5 agitation subscales of the Positive and Negative Syndrome Scale (PANSS), the Clinical Global Impressions (CGI) scale, and time to sedation. No patients receiving risperidone demonstrated any side effects or adverse events, while 1 patient receiving intramuscular treatment with haloperidol developed acute dystonia. One subject receiving risperidone required subsequent treatment with haloperidol for ongoing agitation.

Conclusion: Oral treatment with risperidone and lorazepam appears to be a tolerable and comparable alternative to intramuscular haloperidol and lorazepam for short-term treatment of agitated psychosis in patients who accept oral medications.

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Agitation, characterized by behavioral features such as destructiveness, disorganization, or dysphoria, is a frequent presentation in the psychiatric emergency service.[1] Many clinicians favor intramuscular (i.m.) preparations of high-potency neuroleptics because of the perceived benefits of reliable drug delivery and rapid onset.[2,3] The disadvantages of intramuscular treatment include the facts that injectable medications may be considered coercive and that long-term treatment compliance may be diminished by the side effects of typical antipsychotics, especially extrapyramidal symptoms (EPS).

Atypical antipsychotic medications such as risperidone demonstrate favorable side effect profiles compared with conventional neuroleptics.[2–6] Although atypical antipsychotics may be effective in treating agitation in the psychiatric emergency service, a recent MEDLINE search using keywords *agitation* and *treatment* yielded no published reports to date of their use in this population. One problem in using atypical neuroleptics for rapid tranquilization is that no intramuscular formulations are yet available. This is the first report of the use of an atypical antipsychotic for treatment of psychotic agitation in the psychiatric emergency service. The object of this study was the determination of the relative sedative effect and tolerability of oral risperidone (liquid concentrate) versus intramuscular haloperidol, both in combination with lorazepam, for the emergency treatment of psychotic agitation.

METHOD

Study Design

This was a prospective, nonrandomized, rater-blinded, double-arm study comparing 2 classes of antipsychotic

medications in oral and intramuscular formulation, both in combination with the benzodiazepine lorazepam, for the treatment of agitated patients who presented to a large, urban emergency department. Assessments and provisional diagnoses were made on arrival or shortly thereafter. All patients who were determined to require emergency treatment for psychotic agitation were informed by their treating physician that they would receive emergency medications and were given a choice between the following treatments: risperidone (2 mg liquid concentrate) and oral lorazepam (2 mg) or haloperidol (5 mg i.m.) and lorazepam (2 mg i.m.) (the latter was the standard of care at the study institution). Clinicians read a prepared script to all patients in order to explain medication choices and common side effects. The liquid formulation of risperidone was chosen because of its rapid bioavailability and the ease of checking patient compliance versus the tablet form. The study protocol allowed a repeat dosage of the initial medications to be given if agitation did not subside within 1 hour. An effort was made to obtain urine samples on all patients for toxicology analysis. The raters who assessed efficacy and safety were blinded to the treatment option (interrater reliability, $\kappa > 0.95$). Since both medications are indicated for the treatment of psychosis, the study was approved without informed consent by the Human Subjects Review Board at the Los Angeles County and University of Southern California (LAC + USC) Medical Center, Los Angeles.

Patients

A convenience sample of psychotic patients aged 18 to 65 years admitted to the LAC + USC Medical Center Psychiatric Emergency Service during a 3-month period in early 1999 who required emergency medication for the control of agitation and/or violence were eligible for the study. The following patients were excluded: (1) pregnant women, (2) subjects outside the age range of 18 to 65 years, (3) non–English-speaking subjects for whom translation services were unavailable, and (4) developmentally disabled patients.

Assessments of Efficacy and Safety Profiles

Two scales were used to assess overall efficacy of the 2 different treatment regimens. First, we rated agitation according to 5 directly observable Positive and Negative Syndrome Scale[7] (PANSS) items—excitement, hostility, hallucinatory behavior, uncooperativeness, and poor impulse control. These items were chosen to be directly observable by raters and do not rely on patient reports of symptom severity. The PANSS items were measured initially and at 30 and 60 minutes on a scale ranging from 1 (absent) to 7 (extreme).

Behavioral change after treatment was also rated by the Clinical Global Impressions (CGI) scale.[8] The CGI scores were determined at 15, 30, 60, and 120 minutes using a scale ranging from 1 (very much improved) to 7 (very much worse). Other outcomes noted were the time to sleep (sedation) and the need for repeat doses.

Adverse events were recorded for up to 24 hours. Patients were monitored by study staff for the first 2 hours after enrollment. During hours 2 to 24, subjects were evaluated by psychiatric emergency service or inpatient physician and nursing staff, depending on treatment location during those hours. The presence or absence of EPS was noted by clinicians, particularly akathisia or dystonia, as well as any adverse health outcomes requiring physician intervention. Study physicians also examined patients at 24 hours to determine the presence of EPS.

Table 1. Demographic Characteristics[a]

Variable	IM Haloperidol + IM Lorazepam (N = 30)	Oral Risperidone + Oral Lorazepam (N = 30)
Age, mean (SD), y	37.3 (10.7)	37.6 (11.3)
Men/women, N	16/14	23/7
Race, N		
African American	11	11
White	9	9
Hispanic	8	7
Asian	2	3
Emergency department diagnoses, N		
Psychosis NOS	28	28
Schizophrenia	2	0
Mania	0	2

[a]Abbreviations: IM = intramuscular, NOS = not otherwise specified.

Statistical Analysis

Repeated measures analyses of variance (ANOVA) were used to determine significant changes in PANSS and CGI scales over time. A Greenhouse-Geisser adjustment was made to accommodate small sample sizes. Power was determined at 0.8, with sample size selected to detect a 20-minute difference in onset of sedation between the groups given a 45-minute onset of action with a 25-minute standard deviation. Significance was determined at a level of $p < .05$.

RESULTS

Patient Demography

Thirty patients were enrolled in each treatment group. The background characteristics and diagnoses were similar for patients in both groups (Table 1). The mean agitation scores of both treatment groups were also not significantly different at baseline with mean ± SD PANSS scores of 28.5 ± 5.7 for oral risperidone + oral lorazepam and 27.0 ± 5.1 for intramuscular haloperidol + intramuscular lorazepam. Urine toxicology was performed in 17 of the 60 patients; 2 patients were positive for cocaine, and none was positive for tetrahydrocannabinol (THC), opiates, or amphetamines.

Men were significantly more likely to choose oral medication ($\chi^2 = 5.165$, $p < .023$). Of the patients who received intramuscular treatment (N = 30), 15 (50%) refused oral medication, 9 (30%) were unable to follow verbal instructions, and 6 (20%) specifically requested intramuscular medication. All subjects received lorazepam in combination with the respective antipsychotic drug.

Table 2. Combined Psychotic Agitation Scores Over Time[a]

	Initial			30 Minutes			60 Minutes		
Group	Mean	SD	95% CI	Mean	SD	95% CI	Mean	SD	95% CI
Haloperidol i.m. + lorazepam i.m.	28.5	5.7	26.4 to 30.6	14.0	8.9	10.3 to 16.9	8.2	5.7	6.0 to 10.3
Risperidone p.o. + lorazepam p.o.	26.7	5.2	24.8 to 28.7	15.9	9.6	12.3 to 19.6	10.1	8.2	7.0 to 13.3
Difference (95% CI)	1.8		–1.1 to 4.6	–1.9		–6.3 to 2.9	–1.9		–5.4 to 1.8

[a]The agitation score is the sum of 5 items of the Positive and Negative Syndrome Scale (PANSS)—excitement, hostility, hallucinatory behavior, uncooperativeness, and poor impulse control.
Abbreviation: CI = confidence interval.

Efficacy

The agitation scores of both treatment groups, as assessed by combined PANSS scores, declined significantly at 30 and 60 minutes (repeated measure ANOVA, $F = 118.1$, $df = 2$, $p < .0001$) (Table 2). There were no between-drug group differences noted in the agitation scores, nor did the decreases with time correlate with drug arm or sex of the patient. The patients in both groups showed improvement in all 5 combined PANSS measures (repeated measures ANOVA, $F = 63.22$, $df = 3$, $p < .0001$) with no between-group differences emerging ($F = 0.92$, $df = 3$, $p = .42$) (Table 3). The CGI scores improved from baseline in both treatment groups (repeated measures ANOVA, $F = 35.70$, $df = 3$, $p < .0001$), with no between-group differences (repeated measures ANOVA, $F = 2.15$, $df = 3$, $p = .419$) (Table 4). Thus, both measures of efficacy showed similar improvement with no differences between the 2 treatment groups.

Table 3. Mean Scores Over Time for the 5 Individual Components of the PANSS for Oral Risperidone + Oral Lorazepam Versus IM Haloperidol + IM Lorazepam

Group by Time (min)	Hallucinatory Behavior	Hostility	Uncooperativeness	Excitement	Impulsiveness
Haloperidol t_0	4.7	5.3	5.8	6.0	6.3
Haloperidol t_{30}	2.7	2.2	3.2	2.9	3.2
Haloperidol t_{60}	1.7	1.4	1.5	1.7	1.8
Risperidone t_0	5.1	4.9	5.3	5.9	6.1
Risperidone t_{30}	2.9	2.8	2.7	3.6	3.9
Risperidone t_{60}	1.8	1.7	1.9	2.1	2.2

Table 4. Change in the Clinical Global Impressions (CGI) Score Over Time for Oral Risperidone + Oral Lorazepam Versus IM Haloperidol + IM Lorazepam

	IM Haloperidol + IM Lorazepam			PO Risperidone Liquid + PO Lorazepam		
Change Over Time	Mean	SD	95% CI	Mean	SD	95% CI
15-Minute change	4.21	1.23	3.74 to 4.68	4.17	1.23	3.71 to 4.64
30-Minute change	2.90	0.90	2.56 to 3.24	3.28	1.10	2.86 to 3.70
60-Minute change	2.31	0.60	2.08 to 2.54	2.52	1.09	2.10 to 2.93
120-Minute change	2.21	0.94	1.85 to 2.56	2.10	0.41	1.95 to 2.26

Tolerability

The 2 treatment groups were not significantly different with respect to somnolence. The number of patients awake at 2 hours were 5 for oral risperidone + oral lorazepam versus 2 for intramuscular haloperidol + intramuscular lorazepam. The mean ± SD times to sleep were 43.0 ± 25.1 minutes for oral risperidone + oral lorazepam versus 44.3 ± 25.6 minutes for intramuscular haloperidol + intramuscular lorazepam. No adverse events were reported for the oral treatment group, whereas 1 patient in the intramuscular treatment group developed acute dystonia within 24 hours. One patient receiving oral treatment required intramuscular haloperidol for continued agitation.

DISCUSSION

This pilot study has significant limitations that affect generalizability, including a nonrandomized design and a clear potential for selection bias. The nonrandomized design was necessary given the practicalities involved in obtaining compliance with oral medications. There are possible differences between the patients willing to accept oral medications and those unwilling to accept any medications. We attempted to control for these biases by measuring baseline agitation scores before route of drug administration had been determined. Nonetheless, it is possible that subjects who were less impaired preferentially chose the oral alternative. It is also possible that differences in subjects' responses to treatment type may have "unmasked" study observers, although we disenrolled subjects who articulated which medicine they had received. In spite of these limitations, we do show that a substantial number of patients who in this setting would otherwise have received intramuscular medications were willing to accept an oral alternative. Further, in this population, oral risperidone and oral lorazepam appeared to be equally calming and at least as tolerable as injectable haloperidol and lorazepam. These findings were similar for both male and female psychotic patients.

The concept of rapid tranquilization developed over 20 years ago to indicate treating an acutely psychotic patient in an emergency department setting with high doses of antipsychotic medication so that hospitalization could be avoided. First used were high doses of conventional antipsychotics, typically 100 mg or more of haloperidol.[3,9]

Subsequent studies demonstrated that lower doses are equally sedating but associated with fewer side effects. For example, in one study in which 136 patients were treated with haloperidol administered intramuscularly, intravenously, or orally, the average cumulative dose was 8.2 ± 4.5 mg.[10] The response was favorable in the majority of cases, with agitated behavior alleviated in 113 of 136 patients. In another double-blind study, 27 acutely agitated patients were treated with droperidol (5 mg i.m.) or haloperidol (5 mg i.m.).[11] After 30 minutes, 81% of the patients receiving haloperidol required a second injection, but only 36% of patients treated with droperidol required further doses. Both studies suggest that low doses of high-potency antipsychotics are effective in treating agitation in psychotic patients.

Benzodiazepines are also effective for the treatment of agitation.[12,13] For example, in one study 12 consecutive patients admitted to a psychiatric unit and displaying acute psychotic agitation were treated with clonazepam, 4 to 5 mg i.m. every 30 to 60 minutes.[14] All patients showed a dramatic response, with 11 (92%) patients tranquilized within 1 hour. A number of studies have compared benzodiazepines with antipsychotics for the treatment of agitation.[13,15] In 2 studies of lorazepam versus haloperidol, both treatments were equally sedative, suggesting that lorazepam is a reasonable alternative to haloperidol for the treatment of agitation.[16,17] Benzodiazepines are useful in attenuating acute violence, but do not address the underlying psychotic process. Their use may be reasonable in patients for whom the underlying condition is not known.

Some studies suggest that treatment of agitation with a benzodiazepine plus an antipsychotic might be more sedating than either agent alone.[13] For example, in a randomized, nonblind trial in 68 patients, the combination of 5 mg of haloperidol and 4 mg of lorazepam was superior to the individual drugs and required shorter time for tranquilization and fewer repeat doses.[18] Two recent double-blind studies comparing lorazepam plus haloperidol to each drug alone concluded that combination treatment was superior.[19,20] This may relate to the ability of benzodiazepines to ameliorate akathisia, a common side effect of treatment with dopaminergic blocking drugs that may fuel agitated behavior. However, it also remains unclear if the additive effects are dose-related.

Our result on the short-term beneficial effect of risperidone for the treatment of aggression agrees with other longer term published reports. For example, pilot studies in 9 patients with Parkinson's disease and dementia,[21] 109 elderly patients in nursing homes with dementia-related behavioral disturbances,[22] and 22 patients with dementia and behavioral disturbances[23] showed that risperidone attenuated aggressive symptoms. Retrospective studies on 186 elderly patients with dementia[24] and 41 elderly outpatients with dementia[25] similarly suggest the clinical utility of risperidone for aggression. Finally, the reports of randomized, placebo-controlled studies in 344 patients with dementia,[26] 625 institutionalized elderly patients with dementia,[27] 139 patients with hostility associated with schizophrenia,[28] and 31 patients with behavioral symptoms of autism[29] confirm the safety and effectiveness of risperidone. Thus, atypical antipsychotics like risperidone may be a preferable choice for the treatment of aggression versus typical antipsychotics,[30–33] and initiation of treatment may be appropriate in the psychiatric emergency service setting.

In conclusion, oral risperidone in combination with oral lorazepam may be a useful alternative to intramuscular haloperidol in combination with intramuscular lorazepam for the treatment of psychotic agitation in the emergency setting for those patients able to receive oral medications.

Drug names: clonazepam (Klonopin and others), haloperidol (Haldol and others), lorazepam (Ativan and others), risperidone (Risperdal).

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