Risperidone in the Treatment of Delirium: Results From a Prospective Open-Label Trial

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Background: Effective treatment is necessary to reverse delirium and prevent potentially serious consequences.

Method: Patients were identified for screening by initial chart review of all consecutive admissions to the general medical or surgical wards at the Department of Veterans Affairs hospital and the University of Mississippi Medical Center in Jackson, Mississippi, between November 2000 and April 2002. Medically ill patients with delirium defined by DSM-IV criteria and a Delirium Rating Scale (DRS) score of ≥ 13 were given risperidone, 0.5 mg, twice daily, with additional doses permitted on day 1 for target symptoms. Total day 1 dosage was given daily until the DRS score was ≤ 12; dosage was then decreased by 50% (maintenance dose) and continued until day 6. Daily assessment included DRS, Cognitive Test for Delirium (CTD), and modified Extrapyramidal Symptom Rating Scale. Functional status (Karnofsky Scale of Performance Status; KSPS) and medical burden (Cumulative Illness Rating Scale) were assessed at baseline and day 6.

Results: Ten patients (mean age = 64.7 years) were enrolled. Mean daily maintenance risperidone dosage was 0.75 mg. Mean CTD scores improved from day 1 to the day maintenance dose was initiated ($p < .0005$) and remained improved at day 6 (7.1 ± 2.0 and 16.9 ± 3.0, days 1 and 6, respectively; $p = .0078$). Mean DRS scores improved from day 1 to the day maintenance dose was initiated ($p < .0001$) and remained improved at day 6 (25.2 ± 0.9 and 11.3 ± 1.5, days 1 and 6, respectively; $p < .0001$). Mean KSPS scores improved from 32.0 on day 1 to 45.5 on day 6 ($p = .044$). No patient developed movement disorders. One patient each discontinued because of sedation and hypotension.

Conclusion: Low-dose risperidone can improve cognitive and behavioral symptoms of delirium in medically ill patients.

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Delirium is an acute neuropsychiatric syndrome characterized by disturbances in consciousness, attention, cognition, and perception. These changes represent a significant decline from previous level of functioning and develop over a period of hours or days. Delirium is usually a consequence of one or more general medical conditions. It can also be related to medication, such as drugs with anticholinergic effects,[1–3] or can be a consequence of substance abuse.[4]

Delirium is infrequent in young and middle-aged patients unless associated with substance abuse or in the postoperative period but is common in medically ill elderly. It occurs in approximately 14% to 24% of older patients at hospital admission and in as many as 6% to 56% of patients during hospitalization.[5] Delirium in elderly patients is associated with increased mortality,[6] increased length of hospitalization, and increased risk of institutional placement.[7] Long duration of symptoms is associated with poor functional outcome.[5,8]

Treatment of delirium consists of identifying and concurrently managing underlying medical abnormalities and the associated psychiatric symptoms. Antipsychotics are

considered the drugs of choice in managing symptoms of delirium.[9] Most commonly, high-potency conventional antipsychotics, particularly haloperidol, are used[10]; however, these agents have a much greater liability for movement disorders than do atypical antipsychotics, especially in elderly patients.[11] Three small case series[10,12,13] and a retrospective chart review[10] have reported successful management of symptoms of delirium with the atypical antipsychotic risperidone. We report here results of an open-label prospective trial of the efficacy and safety of risperidone in the treatment of 10 patients with delirium.

METHOD

We conducted an open-label 6-day study of risperidone in the treatment of delirium in hospitalized patients. The local institutional review board approved the study, and informed consent was obtained from the patients' surrogate decision makers, as patients were deemed unable to fully understand and appreciate the issues involved in participating in a drug trial.

Patients were identified for screening by initial chart review of all consecutive admissions to the general medical or surgical wards at the Department of Veterans Affairs hospital and the University of Mississippi Medical Center hospital in Jackson, Mississippi, between November 2000 and April 2002. All patients having confusion, agitation, hallucinations, change in mental status, use of restraints, or diagnosis of delirium as indicated in admission notes of the attending physician were screened by the investigators to determine whether history and clinical findings were consistent with delirium. Patients thus identified were then screened using the Confusion Assessment Method,[14] after which an investigator performed further assessments of delirium for determining study eligibility. After enrollment in the study, patients were treated with risperidone for 5 days. Patients who had no improvement in symptoms of delirium by day 4 according to study assessments were withdrawn from the study. All patients continued to receive usual care for their underlying medical problems throughout the study.

Any medication that could cause delirium and was not deemed essential for the care of the patient was discontinued at study entry.

Patients

Male and female patients aged 18 to 90 years were eligible to enter the study if they had delirium according to the Confusion Assessment Method, met DSM-IV criteria for delirium, and had a score of ≥ 13 on the Delirium Rating Scale (DRS).[15] Patients were excluded from the study if they were already receiving antipsychotic medication or benzodiazepines (not including antiemetics), had delirium caused by alcohol or benzodiazepine withdrawal, had a terminal illness with an estimated survival of a few days or Parkinson's disease, had a history of neuroleptic malignant syndrome or a prior hypersensitivity to risperidone, or if the study would interfere with treatment of their primary medical condition. Patients who were known to have moderate or severe dementia at the time of screening were not enrolled in the study.

Study Medication

On day 1, patients were started on risperidone, 0.5 mg, twice daily. Additional doses (0.5 mg each) could be given on day 1 for treatment of specific psychotic or behavioral symptoms (e.g., hallucinations, delusions, or agitation) as determined by the principal investigator. The total daily dosage of risperidone received on day 1 was given in divided doses twice daily until the DRS score decreased to ≤ 12. The daily dosage was then decreased to 50% of the day 1 dose (the "maintenance dose") and continued for the remainder of the study. The dosing schedule was determined following consultation with Paula T. Trzepacz, M.D., a nationally recognized expert on delirium.

Assessments

Primary efficacy measures were the DRS and the Cognitive Test for Delirium (CTD),[16] administered at baseline and daily throughout the study. The DRS is a 10-item scale used to rate presence and severity of symptoms of delirium (perceptual disturbances, hallucinations, delusions, altered psychomotor behavior, cognitive deficits [as assessed by routine mental status examination], sleep-wake cycle disturbances, and mood lability), as well as onset and variability of symptoms and presence or absence of a temporally associated physical disorder.[15] The CTD is a 30-point test that assesses 5 areas of functioning in delirious patients (orientation, attention span, memory comprehension, conceptual reasoning, and vigilance).[16] Efficacy was also assessed at baseline and at endpoint using the Karnofsky Scale of Performance Status (KSPS),[17] an 11-item scale that assesses physical ability, and the Cumulative Illness Rating Scale (CIRS) total score and severity index score.[18] The CIRS is a brief instrument for assessing health status that comprises clinical ratings of morbidity and impairment in each of 13 major organ-system or disease-specific groups.[19] Ratings are made on a 5-point scale ranging from "none" to "extremely severe."

A slightly modified version of the Extrapyramidal Symptom Rating Scale (ESRS)[20] was used to determine the severity of symptoms of parkinsonism, dyskinesia, and dystonia daily on days 1 to 6. Modifications to the ESRS were omission of subjective parkinsonism ratings, which could not be obtained due to cognitive and perceptual impairment, and omission of gait and posture evaluations, which could not be performed in these nonambulatory patients. Serum albumin levels were obtained at baseline, and electrocardiographic and routine laboratory testing

Table 1. Criteria for Exclusion of Patients From an Open-Label Trial of Risperidone for Delirium (N = 121)

Reason for Exclusion	N	%
Dementia	53	43.8
Prior benzodiazepine	19	15.7
Prior antipsychotic	14	11.6
Terminal illness	15	12.4
Family refused	10	8.3
Parkinson's disease	7	5.8
Physician refused	3	2.5

was obtained at baseline and endpoint. Vital signs were assessed daily.

Patients were observed for other potential adverse effects from risperidone such as sedation, hypotension, gastrointestinal adverse effects, and rash.

Statistical Analysis

We used descriptive statistics to summarize demographics and baseline scores for assessing the patient's delirium rating, cognitive status, functional ability, and medical status. Estimates are reported as mean scores and standard errors (mean ± SE). Efficacy and safety were evaluated in terms of change in mean scores from day 1 to day of maintenance and then to day 6. For parameters for which endpoint values could not be obtained, the last value was carried forward. Statistical significance of changes in DRS, CTD, KSPS, and CIRS scores and frequency of movement disorders were evaluated by conducting repeated-measures analyses using a combination of paired t tests, F tests, and chi-square tests. Hypotheses of no change were tested against 2-directional alternatives using the .05 level of significance.

RESULTS

One hundred thirty-one patients were screened. Of the 121 patients excluded, most had a history of dementia, a terminal illness, or had received either benzodiazepines or antipsychotics before evaluation (Table 1). Ten patients met inclusion criteria and were recruited into the study, of whom 8 completed the trial. Treatment was discontinued on day 3 in 1 patient (case 4) because of severe, aggressively treated congestive heart failure, bradycardia, and worsening of hypotension that had been present since admission; any contribution of risperidone to ongoing hypotension, while possible, could not be either established or excluded. The final (day 6) assessments were performed on day 3 in this patient. Treatment was discontinued on day 4 in another patient (case 7) due to lethargy that began on day 3 and was followed by obtundation; sedation induced by risperidone may have been a contributing factor. The final (day 6) assessments were performed on day 4 in this patient. In both patients, CTD could not be performed because of sedation on the final day in the study.

Eighty percent of the patients were male (mean age = 64.7 ± 4.8 years) (Table 2). The mean number of medications per patient at the time of entry into the study was 10.4 ± 1.5. At study entry, 3 patients were taking medications that could have contributed to delirium (prednisone, fentanyl, and propoxyphene); these could not be discontinued without compromising patient care. In addition, medications with anticholinergic properties, such as digoxin and diuretics, were continued as deemed essential for patient care. The mean serum albumin level at study entry was 2.75 ± 0.19 g/dL.

All of the patients had some degree of behavioral and perceptual disturbances as demonstrated by DRS scores at baseline. The mean score on day 1 for the DRS was 25.2 (range, 21–29; maximum score = 32). Mean scores on day 1 for behavioral and perceptual DRS subscales (range, 0–3) were perceptual disturbances, 2.6 ± 0.3; hallucinations, 1.6 ± 0.3; delusions, 2.7 ± 0.3; and abnormal psychomotor behavior, 2.0 ± 0.4.

Dosing

Mean dosage on day 1 was 1.35 ± 0.13 mg/day (range, 1.0–2.0 mg/day). Mean maintenance dosage was 0.75 ± 0.11 mg/day (range, 0.5–1.50 mg/day). Maintenance dose was reached at a mean of 3.89 ± 0.31 days (range, 3–5 days); 1 patient (case 4) did not reach maintenance dose because he was withdrawn from the study before maintenance dose could be reached.

Efficacy

Improvement occurred from day 1 to day 6 on most clinical assessments in 8 of 10 patients (Table 3). Mean CTD scores improved significantly from day 1 to the day that maintenance dose was initiated (7.1 ± 2.0 and 18.8 ± 2.8, respectively, $p < .0005$) and remained significantly improved at day 6 (7.1 ± 2.0 and 16.9 ± 3.0, day 1 and day 6, respectively, $p = .0078$) (Table 3; Figure 1). Mean DRS scores improved significantly from day 1 to the day maintenance dose was initiated (25.2 ± 0.9 and 10.9 ± 1.1, respectively, $p < .0001$) and remained significantly improved at day 6 (25.2 ± 0.9 and 11.3 ± 1.5, day 1 and day 6, respectively, $p < .0001$) (Table 3; Figure 1). Mean KSPS scores also improved significantly from day 1 to day 6 (32.0 ± 3.9 and 45.5 ± 5.4, day 1 and day 6, respectively, $p = .044$).

Improvement in CTD and DRS scores occurred in the absence of statistically significant change in severity of medical illness from day 1 to day 6 as measured by the CIRS total (28.6 ± 1.4 and 28.5 ± 2.1, day 1 and day 6, respectively, $p = .958$) and severity index scores (4.5 ± 0.4 and 4.2 ± 0.5, day 1 and day 6, respectively, $p = .285$).

Safety

Mean ESRS scores were low throughout the study and decreased from days 1 to 6. On the ESRS parkinson-

Table 2. Baseline Demographics and Clinical Characteristics of Patients Enrolled in an Open-Label Trial of Risperidone for Delirium

Case	Age	Sex	Race	No. of Medications	Presumed Medical Etiology[a]	CAM Score	Serum Albumin Level, g/dL
1	51	F	Black	5	Crohn's disease, anemia	3	2.10
2	53	M	White	11	Lithium toxicity	4	3.00
3	37	F	White	10	Sepsis	4	2.10
4	62	M	White	16	CHF	4	2.70
5	80	M	White	17	COPD	4	2.50
6	57	M	White	5	Hyponatremia/hypokalemia	3	3.80
7	79	M	White	10	Anemia, deep venous thrombosis, pulmonary infiltrate	4	3.30
8	83	M	White	15	Anemia, hip fracture, hypoxia	4	2.60
9	72	M	White	11	Pulmonary	4	2.90
10	73	M	White	4	S/P subdural hematoma evacuation	4	2.10

[a]Most likely etiology of delirium as determined by the attending physician and the investigator at the time of resolution of delirium; all patients had multiple medical illnesses.
Abbreviations: CAM = Confusion Assessment Method, CHF = congestive heart failure, COPD = chronic obstructive pulmonary disease, S/P = status post.

ism scale, scores were low on day 1 and decreased at day 6 (1.9 ± 2.7 and 0.6 ± 0.4, baseline and endpoint, respectively, $\chi^2 = 9.70$, df = 1, p = .002). Scores on the dyskinesia scale were also low on day 1 (0.2 ± 0.6) and decreased to 0 on day 6 ($\chi^2 = 3.49$, df = 1, p = .063). Dystonia scores were 0.0 in all patients at days 1 and 6.

No change occurred in QTc interval from day 1 to day 6 (mean QTc = 436 ± 10 ms and 432 ± 15 ms, day 1 and day 6, respectively). Mild sedation occurred in 2 patients (cases 4 and 7), both of whose underlying medical conditions had deteriorated considerably; thus, factors other than risperidone might have contributed to sedation.

DISCUSSION

This open-label prospective case series demonstrates that treatment of hospitalized patients with low-dose risperidone for 6 days is associated with a decrease in symptoms of delirium and improvement in patient functioning. Risperidone treatment was safe in this population, with no evidence of newly emergent movement disorders during the trial.

Eight of 10 patients improved on most measures of delirium. These findings are consistent with response rates in a previously published study of 11 patients with delirium, in which 7 patients had moderate to marked improvement during treatment with low-dose risperidone.[13] Findings are also consistent with improvements in DRS scores and cognition as measured by the Mini-Mental State Examination in a randomized trial of haloperidol, chlorpromazine, and lorazepam in patients with acquired immunodeficiency syndrome[21]; however, differences in scientific rigor, patient demographics, and clinical characteristics in the 2 studies may limit conclusions that can be reached from this comparison.

Improvement in delirium in our study occurred despite the absence of a decrease in overall medical burden as measured using the CIRS. This finding supports the conclusion that improvement in delirium preceded improvement in total medical illness. However, because the CIRS is not sensitive to rapid change in medical burden, definite conclusions cannot be drawn regarding this issue.

Other than sedation, no adverse events that could be clearly attributed to risperidone occurred in this study. Sedation occurred in 2 patients, leading to study discontinuation in one. In the patient withdrawn from the study due to sedation, risperidone might have been a contributing factor, but multiple intercurrent medical events unrelated to risperidone, including gastrointestinal bleeding and deterioration of respiratory function, were confounding factors. In one patient withdrawn from the study due to congestive heart failure, bradycardia, and hypotension, any contribution of risperidone to hypotension, while possible, could not be either established or excluded; however, multiple confounding factors, including decreased cardiac output and coadministration of other possibly contributory drugs (metolazone, spironolactone, furosemide, carvedilol, and isosorbide mononitrate) make the role of risperidone impossible to determine. Additional studies may further elucidate these safety issues in patients with delirium.

No patient developed new-onset movement disorders, although some patients had movement disorders at baseline. These symptoms most likely resulted from diffuse brain dysfunction associated with delirium, which can affect subcortical structures.[22] The patients who exhibited parkinsonian symptoms and akathisia at baseline improved during the course of the study. This improvement may have been secondary to the improvement in delirium. As reduction of disease-related parkinsonism symptoms in drug-naive psychotic patients has been reported in patients taking risperidone,[23] this improvement may also have been related to risperidone.

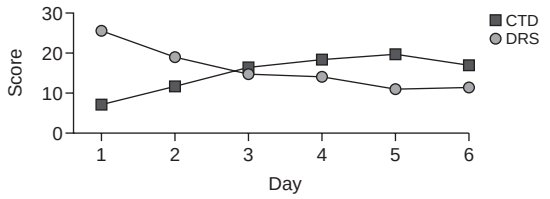
The safety of risperidone demonstrated here supports the use of an atypical antipsychotic rather than a conventional antipsychotic such as haloperidol in patients with

Table 3. Individual and Mean Scores on Clinical Assessments at Day 1 and Day 6 in Patients Taking Risperidone for Delirium

	Test Parameter				
				CIRS	
Score	CTD	DRS	KSPS	Severity Index	Total
Maximum possible	30	32	100	NA	70
Direction of improvement	↑	↓	↑	↓	↓
Total, mean					
Day 1	7.1	25.2	32.0	4.5	28.6
Day maintenance dose reached	18.8*	10.9**	NA	NA	NA
Day 6	16.9†	11.3**	45.5‡	4.2	28.5
Case 1					
Day 1	6	21	40	7.67	23
Day 6	7	15	50	7.67	23
Case 2					
Day 1	7	26	40	3.50	28
Day 6	20	6	60	4.00	24
Case 3					
Day 1	5	29	20	4.40	31
Day 6	20	7	60	3.14	22
Case 4					
Day 1	10	24	50	4.14	29
Day 3[a]	6	19	30	5.00	30
Case 5					
Day 1	2	21	20	3.67	33
Day 6	28	6	60	3.00	24
Case 6					
Day 1	22	24	50	5.25	21
Day 6	30	8	65	4.50	27
Case 7					
Day 1	1	27	20	3.60	36
Day 4[b]	2	15	20	4.40	44
Case 8					
Day 1	11	28	30	4.66	28
Day 6	18	14	40	3.00	27
Case 9					
Day 1	3	27	20	3.88	31
Day 6	22	14	20	3.18	35
Case 10					
Day 1	4	25	30	4.33	26
Day 6	16	9	50	4.14	29

[a]Patient withdrawn from study because of medical complications unrelated to risperidone. All day 6 assessments (except CTD) were performed on day 3 in this patient. Last observation carried forward for CTD.
[b]Patient withdrawn from study because of medical complications unrelated to risperidone. All day 6 assessments (except CTD) were performed on day 4 in this patient. Scoring may have been unreliable due to patient obtundation. Last observation carried forward for CTD.
*$p < .0005$, versus day 1.
**$p < .0001$, versus day 1.
†$p = .0078$, versus day 1.
‡$p = .044$, versus day 1.
Abbreviations: CIRS = Cumulative Illness Rating Scale, CTD = Cognitive Test for Delirium, DRS = Delirium Rating Scale, KSPS = Karnofsky Scale of Performance Status, NA = not applicable.

Figure 1. Mean Scores on the Cognitive Test for Delirium (CTD) and Delirium Rating Scale (DRS) on Days 1 Through 6 in Patients Taking Risperidone for Delirium



delirium, as suggested in previous studies. In one comparative study of conventional and atypical antipsychotics in the treatment of delirium, although efficacy of risperidone and haloperidol were comparable, haloperidol was associated with a higher incidence of movement disorders (66% vs. 20% of patients treated with risperidone).[10] In a study of olanzapine and haloperidol in 22 patients with delirium, 45% of patients treated with haloperidol had either movement disorders or sedation, compared with none of those treated with olanzapine.[24] Drug-induced movement disorders may not only add to medical morbidity but can further confuse an already complicated clinical picture.[10]

Another consideration in the choice of an antipsychotic in the treatment of delirium is its anticholinergic profile. The cumulative anticholinergic burden from various concomitant medications has been implicated in the development of delirium.[3,10] Thus, choosing an atypical antipsychotic with no or low affinity for muscarinic receptors, such as risperidone,[25] might provide an advantage over agents with greater anticholinergic properties. Comparative studies may be necessary to confirm whether atypical antipsychotics with low affinity for muscarinic receptors provide a therapeutic advantage over those, such as olanzapine,[25] with high affinity for these receptors.

Our findings are limited by the open-label design and small number of patients. All of the patients were very ill and were treated with several concurrent medications, which may have resulted in confounding effects. To eliminate some confounding factors, patients with moderate or severe dementia, as well as those given benzodiazepines or other antipsychotics, were excluded from the study. However, as such patients represented most of those screened, it might be argued that the patients in this study were not a representative sample of patients with delirium. The validity of generalizing these results to a wider population of patients with delirium remains to be confirmed in larger double-blind studies, although the efficacy of risperidone in delirium in patients with pre-existing dementia has been previously reported in an open-label series.[10]

In conclusion, results of this open-label study indicate that risperidone is an effective and safe alternative to conventional antipsychotics in the treatment of delirium. The use of risperidone does not negate the need for concurrent nonpharmacologic treatment as well as continued treatment of the underlying medical condition. Randomized controlled studies with a larger sample are indicated to confirm the results of this initial study.

Drug names: carvedilol (Coreg), chlorpromazine (Thorazine, Sonazine, and others), digoxin (Lanoxicaps and others), fentanyl (Duragesic and others), furosemide (Lasix and others), haloperidol (Haldol and others), isosorbide mononitrate (Imdur, Ismo, and others), lorazepam (Ativan and others), metolazone (Zaroxolyn and others), olanzapine (Zyprexa), prednisone (Deltasone and others), propoxyphene (Darvon, Kesso-Gesic, and others), risperidone (Risperdal), spironolactone (Aldactone and others).

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