Risperidone in the Treatment of Patients With Delirium

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Background: The aim of this study was to evaluate the efficacy and safety of risperidone in the treatment of patients with delirium.

Method: We conducted a prospective, multicenter, observational 7-day study in 5 university general hospitals. Sixty-four patients (62.5% male [N = 40]; mean age: 67.3 ± 11.4 years) hospitalized due to a medical condition who met criteria for delirium according to DSM-IV were enrolled in the study. Fifty-six patients received 7 days of treatment or less, while 8 patients continued treatment for more than 7 days. Effectiveness was assessed using the Trzepacz Delirium Rating Scale (DRS), the positive subscale of the PANSS (PANSS-P), the Mini-Mental State Examination (MMSE), and the Clinical Global Impressions scale (CGI). Safety assessment included the UKU Side Effect Rating Scale. Risperidone was administered at the time of diagnosis, and treatment was maintained according to clinical response. Response to treatment was defined as a reduction in DRS score to below 13 within the first 72 hours. Data were gathered from April to December 2000.

Results: Risperidone (mean dose = 2.6 ± 1.7 mg/day at day 3) was effective in 90.6% (58/64) of the patients and significantly improved all symptoms measured by the scales from baseline to day 7 (mean scores: DRS, 22.5 ± 4.6 at baseline to 6.8 ± 7.0 at day 7; PANSS-P, 21.5 ± 8.8 to 10.1 ± 7.3; MMSE, 13.1 ± 10.9 to 26.4 ± 8.9; and CGI, 4.5 ± 0.9 to 1.9 ± 1.2) (Friedman test, $p < .001$ in all cases). Two patients (3.1%) experienced adverse events, but none showed extrapyramidal symptoms.

Conclusions: Low-dose risperidone proved to be a safe and effective drug in the treatment of symptoms of delirium in medically hospitalized patients. These data provide the rationale for a prospective randomized controlled trial.

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Delirium, or acute confusional state, is an organic psychiatric syndrome leading to fluctuating levels of consciousness and impairment of attention, cognition, perception, and behavior.[1] Patients often experience hallucinations and delusions such as paranoia (20%). The prevalence of delirium in medically hospitalized patients ranges from 10% to 30%,[2] and it is associated with both increased mortality[3] and longer hospitalization,[4] particularly if not diagnosed and treated. As a result, it is reported that delirium has increased hospital costs and that patients require additional medical care after discharge (rehabilitation, institutionalization, nursing home care).[5]

Conventional antipsychotics (phenothiazines and butyrophenones) have been the drugs of choice in the symptomatic management of delirium.[2] Phenothiazines may produce anticholinergic side effects, which can lead to an impairment of cognitive functioning, sedation, hypotension, or even worsening of delirium.[6] Butyrophenones, particularly haloperidol, a high-potency dopamine D_2 receptor blocker, have been the gold standard for treatment of delirium due to the few anticholinergic side effects, low levels of orthostatic hypotension and sedation, and availability in many dosage forms.[7] However, haloperidol can cause neurologic side effects, especially extrapyramidal symptoms (EPS) such as parkinsonism, dystonia, and neuroleptic malignant syndrome,[7,8] and also may lengthen the QT interval, which can lead to torsades de pointes, even with oral doses.[9]

The newer atypical antipsychotics with a different receptor blocking profile (risperidone, olanzapine, quetiapine, ziprasidone) offer the benefit of lower rates of EPS, which has led some physicians to use these agents for the treatment of delirium. Several case reports have examined the treatment of delirium with risperidone,[10,11] quetiapine,[12] and olanzapine.[13] Recently, an open pilot trial was published using olanzapine for delirium with a small sample.[14] However, larger clinical trials of the new antipsychotics for the treatment of patients with delirium have yet to be published, although such studies have been recommended in the American Psychiatric Association guidelines for treating delirium.[2] Currently, the use of risperidone for delirious patients is an off-label indication use according to U.S. Food and Drug Administration regulations. Therefore, this prospective, multicenter, observational study aimed to determine the efficacy and safety of risperidone in the treatment of mental symptoms

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and behavioral disturbances associated with delirium in medically hospitalized patients.

METHOD

Patients

Patients were candidates for the study if they had been hospitalized due to a medical condition, had a diagnosis of delirium according to the criteria of the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV),[15] were older than 18 years, and were suitable candidates for oral administration of medication.

Exclusion criteria included pregnancy and lactation, delirium due to drug abuse or abstinence immediately following drug abuse, delirium associated with physical restraint due to psychomotor agitation, delirium in the context of a terminal event (the patient is expected to die within 24–48 hours), previous psychotic disorder, and a history of neuroleptic malignant syndrome, epilepsy, or Parkinson's disease. Patients with sensory impairment including severe visual or auditory impairment and those on an absolute diet were also excluded.

The study was approved by the Ethical Review Board. Patients' legal representatives provided written informed consent for them to participate in the study, and the investigation was conducted following the international and local guidelines for pharmacoepidemiology studies.

The study was conducted in general hospitals of 5 cities in Spain. Data were gathered from April to December 2000.

Measurements

The following scales were used to assess efficacy and side effects associated with risperidone treatment: the Trzepacz Delirium Rating Scale (DRS),[16] the positive subscale of the Positive and Negative Syndrome Scale (PANSS-P),[17] the Mini-Mental State Examination (MMSE),[18] the Clinical Global Impressions scale (CGI),[19] and the UKU Side Effect Rating Scale.[20]

The Trzepacz DRS is the most widely used delirium assessment instrument. It includes 10 items measuring the presence and severity of a broad range of delirium symptoms such as perceptual disturbances (illusions or hallucinations), delusions, psychomotor changes, affective lability, and disturbances of the sleep-wake cycle. The maximum score is 32. A score of 13 or above identifies patients as having delirium.[16]

The PANSS-P subscale measures the following psychotic symptoms: disorganized thoughts, hallucinations, delusions, grandiosity, hostility, excitement, and suspiciousness. For each item, severity is scored on a 7-point scale.[17]

The MMSE is the current standard scale for measuring cognitive functions. It assesses orientation as well as cognitive capacity. A score of less than 24 has been considered the cutoff for clinically significant cognitive impairment.[18]

The CGI is a rating of the severity of psychotic symptoms on a scale from 0 (no disease) to 7 (extremely severe illness).[19]

Safety was measured with the UKU Side Effect Rating Scale. It is divided into 4 subscales (psychic, neurologic, autonomic, and other side effects) that measure 48 symptoms. The neurologic subscale assesses dystonia, rigidity, hypokinesia, hyperkinesia, dyskinesia, tremor, and akathisia. Each symptom is scored on a 4-point scale, based on its presence and severity. All symptoms present are classified as "improbable," "possible," or "probable" depending on their supposed connection to risperidone treatment.[20] Other adverse events observed by the investigators during the study were also registered.

Severity of illness on the day of diagnosis was estimated by each site investigator and a consultant physician, using the medical status profile based on chart comments and laboratory data. Severity was scored on a 3-point scale (1 = mild, 2 = moderate, and 3 = severe) for the severity of each patient's disease. This procedure allowed the physician to categorize each specific illness according to the chart. Categorical presumed etiologies included systemic illnesses (infections, neoplasm, postoperative state), as well as metabolic, cardiopulmonary, and central nervous system disorders.

Procedures

Each patient was evaluated by each site investigator at baseline using the DRS, PANSS-P, MMSE, and CGI. The UKU was also used for excluding adverse events. One hour later, all of the scales except for the PANSS-P and MMSE were administered again, and 2 hours after baseline, another complete psychopathologic examination was performed. Patients were evaluated with all of the scales every day for 1 week. Day 7 of treatment was considered the endpoint of the study. Response to treatment was defined as a reduction in DRS score to below 13 within the first 72 hours.

Risperidone was administered in oral liquid form (1 mg = 1 mL). Daily dosages started at 1.25 mg (patients older than 65 years) or 2.5 mg (patients younger than 65 years) at baseline evaluation and were raised depending on the patient's clinical response during the next 2 hours. The dosages were given in a twice-a-day regimen. These quantities of risperidone are considered low doses, since for schizophrenia the modal dose of risperidone is 4 to 6 mg/day.[21] No other antipsychotic drugs were administered throughout the study.

Other concomitant medications given during the study included psychotropic drugs used by patients before delirium began and medications prescribed by physicians for nonpsychiatric diseases.

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Statistical Analysis

Primary analyses were performed on the 64 subjects included in the study and were conducted at least once during drug treatment. Analysis of efficacy was performed on the intent-to-treat population, using the last available value of each studied variable. Nonparametric paired tests (Friedman test 2-way analysis of variance and Wilcoxon test) were used. There was also a tolerance analysis of all patients who began treatment with risperidone. Interrater reliability among the 7 site investigators was established for all of the scales (kappa coefficient = 0.90). The statistical package SPSS, version 10.0,[22] was used to perform all of the described analyses.

RESULTS

Baseline Characteristics of Patients and Withdrawals

A total of 64 of 85 delirium patients evaluated were enrolled in the study. Between 15 and 18 patients were recruited at each site. The data for 21 patients were excluded from the study for the following reasons: oral administration of medication was not suitable for 9 patients, the etiology of delirium in 5 patients was drug abstinence, 4 patients were experiencing a terminal event, and 3 patients required physical restraint. Clinical features of the sample were as follows: 40 patients (62.5%) were male, mean age was 67.3 ± 11.4 years, and mean weight was 69.8 ± 10.8 kg (155.1 ± 24.0 lb). Etiologies of delirium were presumed in 71.8% [N = 46] of the patients and unspecified in the remaining 28.2% [N = 18]. Many patients had multiple etiologies and some (N = 20, 31.2%) had a single definite or probable etiology for delirium. The presumed etiologies were as follows: systemic illnesses (postoperative state, N = 24 [37.5%]; infections, N = 9 [14.1%]; neoplasm, N = 3 [4.7%]; severe trauma, N = 5 [7.8%]), central nervous system disorders (head trauma, N = 3 [4.7%]; vascular disease, N = 1 [1.6%]; degenerative disease, N = 6 [9.4%]); metabolic disorders (renal failure, N = 3 [4.7%]; endocrinopathy, N = 2 [3.1%]; electrolyte imbalance, N = 2 [3.1%]; hepatic failure, N = 1 [1.6%]); and cardiopulmonary disorders (respiratory failure, N = 7 [10.9%]; congestive heart failure, N = 4 [6.3%]; myocardial infarction, N = 2 [3.1%]).

Severity of medical conditions was in the moderate-to-severe range for the study group (mean = 2.6 ± 3.3; range, 1.85–2.97).

Twenty-six percent of patients took other psychoactive drugs during the study, including anxiolytics (N = 7, 10.9%), antidepressants (N = 5, 7.8%), anticonvulsants (N = 2, 3.1%), and others (N = 3, 4.7%). The dosages of these psychoactive drugs were kept fixed during the study, and all had been prescribed before the onset of the study.

Sixty-one patients (95.3%) were receiving medical treatment: analgesics, antihypertensive and cardiovascular medication, antimicrobials, immunosuppressive and corticosteroid agents, antineoplastic drugs, antiasthmatic agents, anesthetics, gastrointestinal medications, hormones (including insulin), and others.

A few patients left the study early; reasons for leaving were as follows: 1 patient (1.6%) suffered from a tonic seizure; 3 patients (4.7%) left due to a lack of response at day 3, at which point they began treatment with haloperidol; and 2 patients (3.1%) died due to medical events compatible with their previous diseases (patient 1: diabetes, heart attack, angina pectoris, coronary bypass; patient 2: cor pulmonale, chronic obstructive pulmonary disease, and severe respiratory infection with respiratory failure). Recently, the manufacturer of risperidone issued a warning to all U.S. physicians about the risk of cerebrovascular adverse events with risperidone treatment in the elderly demented population. No adverse cerebrovascular events were noted in our study population.

Drug Treatment

The mean daily dose of risperidone for the first 24 hours of treatment was 2.6 ± 1.3 mg. The dose remained stable for 3 days as maintenance treatment (day 3: 2.6 ± 1.7 mg/day), decreasing progressively to 1.5 ± 0.8 mg/day at day 7.

Almost 88% (56/64) of the patients were treated for 1 week or less (7 days: N = 25, 39.0%; 6 days: N = 3, 4.7%; 5 days: N = 5, 7.8%; 4 days: N = 7, 10.9%; 3 days: N = 4, 6.3%; 2 days: N = 8, 12.5%; 1 day: N = 4, 6.3%). The remaining 12% (8/64) of the patients continued taking risperidone until delirium symptoms subsided (8 days: N = 1, 1.6%; 9 days: N = 3, 4.7%; 10 days: N = 1, 1.6%; 13 days: N = 3, 4.7%).

Efficacy

With response to treatment defined as a reduction in DRS score to less than 13 within the first 72 hours, 90.6% (58/64) of patients responded. There was a significant reduction of 15.8% in DRS total score during the first 24 hours, 31.1% within 48 hours, and 45.3% within 72 hours (Friedman test, $p < .05$).

Risperidone was associated with a significant improvement on all measures from baseline to endpoint. Thus, mean DRS scores for the total sample were 22.5 ± 4.6 at baseline, 12.3 ± 7.3 at day 3, and 6.8 ± 7.0 at the end of the study (Figure 1). There was a significant decrease from baseline throughout the study period (Friedman test 2-way analysis of variance: $p < .001$) and from baseline to endpoint (Wilcoxon: $p < .05$).

The mean PANSS-P score declined from 21.5 ± 8.8 at baseline to 12.9 ± 7.7 at day 3 and 10.1 ± 7.3 at day 7 (Wilcoxon: $p < .001$) (Figure 2). There was also a significant improvement between baseline and each subsequent assessment (Friedman: $p < .001$).

Figure 3 shows MMSE scores from baseline (13.1 ± 10.9) to day 3 (21.9 ± 9.9) and day 7 (26.4 ± 8.9),

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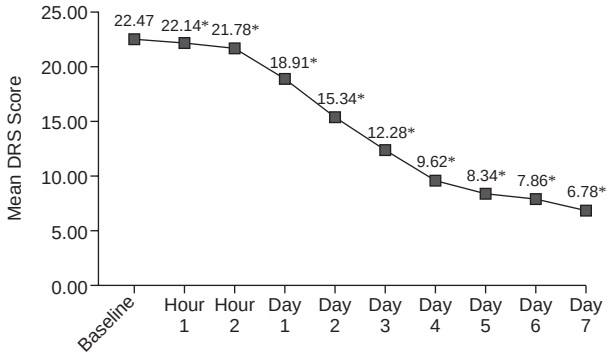
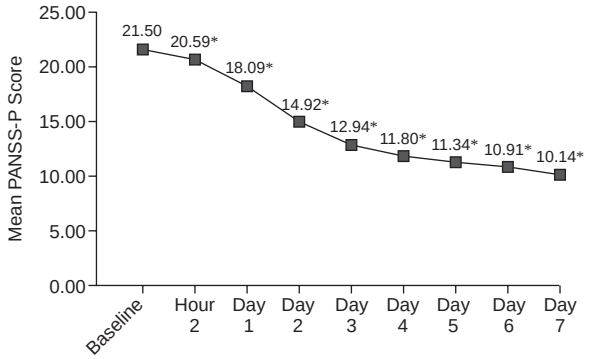
Figure 1. Change in Delirium Rating Scale (DRS) Scores From Baseline to Day 7



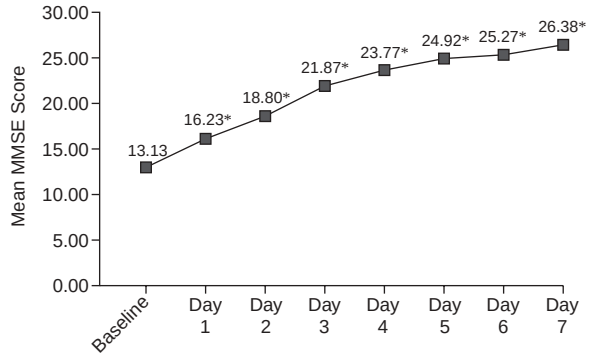
*p < .001 (Friedman test).

Figure 2. Change in Scores on the Positive Subscale of the Positive and Negative Syndrome Scale (PANSS-P) From Baseline to Day 7



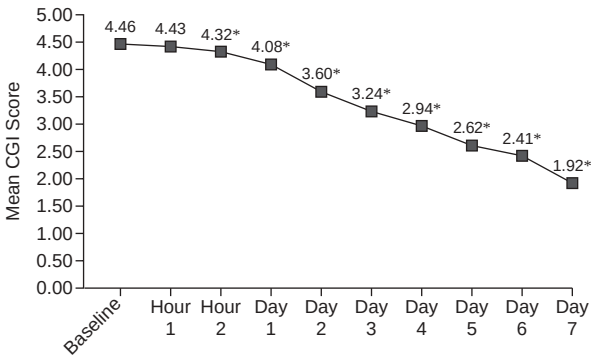
*p < .001 (Friedman test).

Figure 3. Change in Mini-Mental State Examination (MMSE) Scores From Baseline to Day 7



*p < .001 (Friedman test).

Figure 4. Change in Clinical Global Impressions Scale (CGI) Scores From Baseline to Day 7



*p < .001 (Friedman test).

demonstrating improvement in cognitive scores after risperidone treatment (Wilcoxon: $p < .001$ from baseline to endpoint; Friedman: $p < .001$ from baseline throughout the study period).

The mean CGI scores decreased significantly from 4.5 ± 0.9 at baseline to 3.2 ± 1.2 at day 3 and 1.9 ± 1.2 at day 7 (Wilcoxon: $p < .001$) (Figure 4). The Friedman test also showed significant results, with scores decreasing throughout the study period ($p < .001$).

Safety

Scores on the neurologic subscale of the UKU showed that risperidone was well tolerated during the treatment. The scores declined significantly from baseline (1.2 ± 0.3) to day 3 (1.1 ± 0.1) (Wilcoxon: $p < .05$) and day 7 (1.0 ± 0.1) (Wilcoxon: $p < .002$). No patients needed anticholinergic medication during the study.

Unrelated to EPS, 2 patients (3.1%) experienced drowsiness and 1 (1.6%) experienced nausea. Additionally, 2 other patients (3.1%) experienced an adverse event. One suffered from acute renal failure, which was considered by the physicians to be remotely related to risperidone use and related to previous disorders, so the patient continued taking the medication in the same dosages. The other suffered from a tonic seizure doubtfully related to risperidone, considering the basal medical status of the patient.

DISCUSSION

This prospective, multicenter, observational clinical study provides evidence that medically hospitalized patients with delirium can be treated effectively and safely with low doses of risperidone.

Before the underlying cause of the delirium symptomatology was treated, the clinical improvement of the sample was accomplished within the first 24 to 48 hours after administration of risperidone (15.8% and 31.1% re-

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duction in DRS total score, respectively), and reduction in DRS score reached 45.3% at 72 hours, with a rate of response of 90.6% of patients. These significant reductions could be considered a good indicator of improvement, similar to that found in a study using haloperidol.[23]

Additionally, the low doses of risperidone used in the study resulted in good clinical response. The dosage decreased almost 45% from baseline to the seventh day of the study. This finding implies that good results are achieved more quickly and with doses lower than for psychotic symptoms caused by other disorders, thus lowering the risk of adverse events. Low doses of risperidone have also been used to reduce agitation in demented patients (0.5–1.25 mg/day)[24] and patients with geriatric psychosis (2.1 ± 1.4 mg/day).[25]

The efficacy and safety results measured with the DRS, positive subscale of the PANSS, MMSE, CGI, and UKU lead us to conclude that risperidone is a good therapeutic alternative to conventional antipsychotics in the treatment of patients with delirium. In our sample, risperidone treatment resulted in a significant improvement in both psychotic and other symptoms associated with delirium, with an adequate tolerability and safety profile. These improvements were achieved with few adverse effects, which is significant in light of the fact that delirium is mostly a disorder of elderly people, who are especially vulnerable to EPS. Other studies have also reported a similar lack of adverse events with risperidone treatment in the elderly, showing a low rate of cognitive impairment, EPS, and tardive dyskinesia[26] without risk of QT dispersion.[27]

Our results are promising compared with published data on gold-standard haloperidol treatment of delirium in terms of both efficacy and lack of EPS. The drugs have similar time to peak response in delirium treatment, but in our sample, no extrapyramidal adverse events were found. This finding compares favorably with data reported by Someya et al.[7] in which 39% of participating facilities in a survey thought haloperidol caused EPS in the treatment of delirium. Data concerning the incidence of EPS with other high-potency antipsychotics in the treatment of delirium are unavailable.

This study had several strengths, including the following: it was the first clinical study to use risperidone as a treatment for delirium patients, it had the largest sample of patients with delirium treated with an atypical antipsychotic, and it used a daily assessment of symptoms with several validated and standardized scales.

There were, however, several limitations to the study. First, it was a prospective observational clinical study and did not have a comparison treatment group in a randomized double-blind clinical trial, which is considered the gold standard for the assessment of the efficacy of treatments.[28] Second, agitated patients who required physical restraint were not included in the study, which could present selection bias because the most severely ill patients in terms of psychomotor condition were not among the studied sample. Third, patients unable to use oral drugs were excluded because there is no fast-acting parenteral formulation of risperidone available, which would have been necessary for the management of agitated patients and those who were on an absolute diet. This exclusion criterion may have created a selection bias. Fourth, although our study used the largest sample of delirium patients treated with a new antipsychotic drug to date, an even larger sample may be necessary. Fifth, uncontrolled nonpharmacologic strategies such as nursing care or family interventions in the management of delirium patients constitute a further limitation,[29] although these are not generally considered to be primary treatments for delirium.[30]

Despite the limitations of the study, our data provide the rationale for a prospective randomized controlled trial to confirm the usefulness of this drug to treat patients with delirium due to a medical condition.

In summary, we found that symptoms of delirium in medically hospitalized patients may be treated in medical settings efficaciously and safely using risperidone at a mean dose of 2.6 ± 1.7 mg/day, which is far lower than the doses required for the treatment of schizophrenia. While we demonstrated that low doses of risperidone are useful in the management of delirium, further studies are needed with a controlled, double-blind design to compare risperidone with both conventional and other atypical antipsychotics in order to confirm the efficacy and safety of this drug.

Drug names: haloperidol (Haldol and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), ziprasidone (Geodon).

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