Safety and Tolerability of a Rapidly Escalating Dose-Loading Regimen for Risperidone

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Background: Risperidone is an "atypical" antipsychotic with strong binding affinity for dopamine-2 and serotonin-2 receptors. Risperidone is often used to treat hospitalized patients who have acute psychotic decompensation, and the therapeutic target dose commonly used is 2 to 6 mg/day. The most common clinical practice is to titrate the dose of risperidone to the target therapeutic dose over several days. This study investigated the safety and tolerability of a rapid oral-loading regimen for risperidone developed to achieve therapeutic doses of this antipsychotic within 24 hours.

Method: Rapid-loaded risperidone was initiated with 1 mg. Subsequent doses were increased by 1 mg every 6 to 8 hours up to 3 mg. Dose increases were contingent on tolerance of last administered dose.

Results: Of a sample of 11 consecutive inpatients admitted to an acute psychiatric facility who were treated with this protocol, 7 tolerated the most rapid titration, achieving a standing dose of 3 mg b.i.d. in 16 hours. Three required a slightly slower titration and achieved this target dose in 24 hours. One patient could not tolerate the 3-mg dose but tolerated a standing regimen of 2 mg t.i.d. No patient experienced serious extrapyramidal side effects, sedation, or any other adverse event during the rapid titration, and in no case did risperidone have to be discontinued.

Conclusion: These results suggest that aggressive dosing of risperidone is well tolerated in most psychiatric inpatients.

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Patients admitted to hospitals for acute psychotic decompensation often exhibit prominent "positive" psychotic symptoms. These patients frequently also exhibit psychotically driven agitation and aggression. High-potency typical antipsychotics such as haloperidol have traditionally been used in this population to induce a rapid reduction in positive psychotic symptoms and in the associated agitation and aggression that may accompany them.

Risperidone is considered an "atypical" antipsychotic. It is distinct among this family of antipsychotics for having potent binding affinity for dopamine-2 (D_2) receptors that is comparable to that of haloperidol.[1] Furthermore, risperidone produces fewer extrapyramidal side effects than haloperidol at therapeutic doses.[2] Risperidone has been shown to be more efficacious than haloperidol in treating positive psychotic symptoms.[3] Risperidone has also been shown to improve agitation and aggression, and these effects may be independent of its antipsychotic effects.[4] Therefore, risperidone represents a useful medication for the treatment of patients hospitalized because of acute psychotic symptoms. For these patients, improvement of their symptoms in a rapid fashion is an important goal. Under such circumstances, medications that can be administered without an extended titration period are advantageous. Haloperidol and other high-potency neuroleptics are typically administered at full therapeutic doses without the need to titrate. Risperidone has a propensity to induce orthostatic hypotension owing to strong blockade of α_1 adrenoceptors.[5] Therefore, it is common practice to start patients on a low dose of risperidone and to escalate the dose to the target dose over the course of several days.[6] Such a dose titration is consistent with the manufacturer's recommendation.[7] It is reasonable to assume that the earlier therapeutic doses of risperidone can be attained, the sooner therapeutic effects may be produced. On the other hand, rapid therapeutic dosing may induce excessive side effects compared with less rapid dose titration. This study investigated the safety and tolerability of a rapidly escalating dose-loading regimen for risperidone that was developed to achieve therapeutic doses of this antipsychotic rapidly among patients with psychosis admitted to a psychiatric inpatient unit. An upper target dose of 6 mg/day of risperidone was selected on the basis of recent prescribing trends in treating psychotic patients with such a dose in contrast to earlier trends, which saw the frequent use of doses above 6 mg/day.[8]

METHOD

We report on unmedicated patients admitted to the Neuropsychiatry and Behavioral Medicine Unit at the University of California, San Diego Medical Center between August and October 1998 who had psychotic symptoms and were considered appropriate for treatment with

an escalating-dose, rapid-loading regimen of risperidone. Exclusion criteria included evidence of previous intolerance to risperidone, refusal to consent for risperidone, preexisting evidence of hypotension, and age greater than 55 years. Concomitant medication such as lorazepam was administered as considered appropriate on the basis of the symptoms of individual patients.

To assess for evidence of orthostatic hypotension, the nursing staff measured supine and standing blood pressure immediately prior to the first oral dose of risperidone and 1 to 1.5 hours after each dose (based on peak plasma load of risperidone) during the escalating-dose protocol. At these timepoints, the nursing staff also documented the patients' subjective sense of light-headedness and other adverse events by asking patients an open-ended question, "How are you feeling?" If the patient did not spontaneously report light-headedness, the nursing staff specifically inquired as to whether the patient felt light-headed or had any other adverse experience since the last dose of risperidone.

The escalating-dose risperidone loading protocol involved oral administration of risperidone at 6- to 8-hour intervals beginning with a dose of 1 mg. At each subsequent timepoint, the dose was increased by 1 mg providing that the patient exhibited no objective or subjective evidence of orthostatic hypotension, defined as an orthostatic blood pressure drop of 15 mm Hg or more or a report of significant light-headedness. If the patient did exhibit significant orthostatic hypotension, light-headedness, or any other adverse event, a clinical decision was made whether to continue administering risperidone at the same dose, at a lower dose, or switch to another drug if appropriate. If blood pressure dropped 15 mm Hg or more or if patients reported significant light-headedness or any other adverse event after 2 consecutive administrations of any dose of risperidone, a clinical decision was made whether to continue administering risperidone at a lower dose or switch to another agent. Once a dose of 3 mg of risperidone was achieved without producing orthostatic hypotension, light-headedness, or any other significant adverse event, a standing dose of risperidone, 3 mg twice per day, was prescribed.

RESULTS

Eleven patients (5 men and 6 women) received the escalating-dose regimen of risperidone during a 3-month period. No subject was excluded owing to orthostatic hypotension or light-headedness prior to titration. The mean age of patients was 38.9 years (range, 29–53 years). Seventy-three percent of subjects were white, 18% were Hispanic, and 9% were African American. None of the patients were medication naive; all except 2 were medication free prior to risperidone treatment. The medication-free interval for all subjects ranged from 0 to 48 months (mean = 5.3 months). The DSM-IV[9] diagnoses of these patients at discharge were as follows: schizophrenia (9 patients), bipolar disorder with an acute manic episode with psychotic features (1 patient), and major depressive disorder with psychotic features (1 patient). Concomitant medication administered during the risperidone load included lorazepam (5 patients; mean dose = 1.7 mg; dose range, 1–3 mg) and fluoxetine, 20 mg (1 patient).

No patient required discontinuation from risperidone. Seven of the 11 patients tolerated the most rapid dose escalation, achieving a dose of 3 mg in the minimum of 3 dosings (16 hours), and exhibited no significant subjective or objective evidence of orthostatic hypotension or other side effects. Three other patients exhibited mild-to-moderate evidence of orthostasis during the titration. Two of these patients exhibited orthostatic blood pressure gaps (17 and 19 mm Hg), without light-headedness, while receiving the 2-mg dose. In both these cases, this effect was resolved after a subsequent dose of 2 mg was administered, and the patients remained below the cutoff when they later received 3 mg. One patient displayed evidence of mild emergent orthostatic hypotension on the basis of an orthostatic blood pressure gap without light-headedness after receiving the 3-mg dose. Again, this completely resolved when a subsequent dose of 3 mg was given 6 hours later and did not reemerge for subsequent doses of 3 mg. Three patients therefore were able to tolerate the targeted titration to a dose of 3 mg within a 24-hour period. In one other patient who experienced light-headedness but not an increased orthostatic blood pressure gap emerging at 3 mg, the symptoms persisted at subsequent doses of 3 mg, and the patient was ultimately prescribed a standing dose of 2 mg t.i.d., which was well tolerated. Thus, 1 patient (9%) was unable to tolerate the rapidly achieved 3-mg dose. Seven patients (64%) tolerated the maximal titration rate of 16 hours, and 3 patients (27%) tolerated at a slightly less-than-maximal titration (24 hours).

None of these patients demonstrated any notable extrapyramidal side effects during their treatment, and therefore, no patient required adjunctive anticholinergic medication. One patient exhibited a syndrome consistent with akathisia, which emerged while the patient was receiving a standing dose of 3 mg b.i.d. of risperidone days after the rapid titration was successfully administered. This akathisia remitted with reduction of the dose of risperidone to 3 mg/day (2 mg every morning and 1 mg at night). Moderate daytime sedation was exhibited by 2 of the 8 subjects after reaching a standing dose of 3 mg b.i.d., and for these subjects, the dose of risperidone was decreased after the first 72 hours of inpatient treatment with resolution of the sedation.

Case Report

Mr. A, a 32-year-old man with a preexisting diagnosis of schizophrenia (paranoid type) and a history of multiple

hospitalizations for acute psychotic exacerbation, was picked up by local police for disturbing the peace by yelling at people in public and acting in a bizarre, agitated manner. This patient admitted to not taking his prescribed antipsychotic (haloperidol) for several months. He denied alcohol or drug use, and results of a urine toxicology screen obtained at admission were negative. At initial assessment, the patient exhibited an extremely disorganized thought process as well as agitation. His Global Assessment of Functioning (GAF)[9] score was 25 at admission. He received the risperidone loading regimen and tolerated it without incident, achieving a standing dose of 3 mg within 18 hours, at which time a standing dose of 3 mg b.i.d. was prescribed. The patient's agitation resolved in the first 24 hours, and his disorganized thinking improved over the first 72 hours of his admission. By the fourth day of his admission, delusional thinking and withdrawn behavior emerged as the patient's main symptoms. On day 5, the patient's risperidone dose was lowered to 2 mg b.i.d. to reflect his decreased positive psychotic symptoms and more prominent negative psychotic symptoms. On day 11, the patient was discharged to a day-treatment program with risperidone, 2 mg b.i.d., with a GAF score of 55.

DISCUSSION

Recent prescribing trends have favored risperidone doses of 6 mg/day or lower for patients with psychosis. Many clinicians routinely use doses lower than 6 mg/day as a target therapeutic dose, and there is clinical[6] and pharmacodynamic[10] evidence that optimal therapeutic effects can be produced with doses less than 6 mg/day. Despite this, 6 mg/day of risperidone continues to be a dose frequently selected by physicians, particularly when treating acute exacerbations of psychotic disorders in an inpatient setting. The optimal therapeutic dose for acute psychosis remains to be elucidated, and this study did not seek to address this issue; rather, the purpose was to investigate the safety and tolerability of aggressive titration of risperidone to therapeutic doses in an inpatient setting. By using an upper target dose of 6 mg/day, this study provides data encompassing the commonly used therapeutic dose range of 2 to 6 mg/day.[8] The loading regimen described in this study can be easily used to titrate to doses lower than 6 mg/day in a similar fashion.

The results of this study show that a target daily dose up to 6 mg/day of risperidone can be achieved safely in most acutely psychotic inpatients within 24 hours. This is at least 2 days earlier than the time it would take to achieve 6 mg/day and at least 1 day earlier than the time taken to achieve 4 mg/day according to the dose titration regimen commonly used, which is based on the manufacturer's earlier dosing recommendations of starting with 1 mg twice per day and increasing by 1 mg twice per day each day.[7] This time difference to achieve therapeutic doses is significant when dealing with acutely psychotic, hospitalized patients for whom improvement in psychosis is an urgent goal.

In this escalating dose regimen, 10 of 11 patients were able to reach the upper target dose of 6 mg/day within the first 24-hour period. One patient experienced moderate akathisia on day 5, which was resolved by decreasing the standing dose of risperidone, but no other patient experienced any clinically apparent extrapyramidal side effects with this regimen, and none of the patients required concomitant anticholinergic medication to symptomatically control extrapyramidal symptoms during their acute hospitalization. This is in contrast to our experience with high-potency neuroleptics; on informal chart review, we have found that approximately 39% of psychotic inpatients treated with typical antipsychotics at our facility require concomitant anticholinergic medication such as benztropine during their acute hospitalization, and about 28% are discharged with anticholinergic medication.

The present study is limited because of the small sample size. It is also important to emphasize that patients above 55 years of age were not included and that no subject was antipsychotic naive, although most of them were not medicated with antipsychotics at the time of undergoing risperidone titration. All of the subjects had previous episodes of acute psychosis (i.e., no first episodes). Therefore, caution must be exercised when extrapolating these findings to children, the elderly, and patients experiencing a first psychotic episode and possibly to patients of East Asian background.[11]

Drug names: benztropine (Cogentin and others), haloperidol (Haldol and others), lorazepam (Ativan and others), risperidone (Risperdal).

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