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Brief Report

Risperidone Treatment of Drug-Related Psychosis in Patients With Parkinsonism

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Summary: Risperidone, a novel neuroleptic with approximately equal D_2 and $5HT_{2A}$ receptor blocking properties, has been used to treat drug-related hallucinations in patients with Parkinson's disease. However, the results of only small numbers of patients have been reported with the drug demonstrating limited usefulness. We report our experience with this drug in 39 patients (25 women and 19 men) with parkinsonism. Monitored clinical data included duration of disease, Hoehn and Yahr score, Mini-Mental State Score, Unified Parkinson's Disease Rating Scale (UPDRS) prior to drug administration and after 3 and 6 months of treatment, and response to treatment. Twenty-three patients with Parkinson's disease had either complete or near-complete resolution of hallucinations whereas an unsatisfactory response (N = 6) or worsening of parkinsonism (N = 6) was noted in 12 patients, only six of whom had Parkinson's disease. Excluding patients with diffuse Lewy body disease, there was no significant worsening of the UPDRS scores after either 3 or 6 months of treatment. The presence of dementia did not predict response to treatment. Our results suggest that risperidone is a useful treatment for hallucinations in patients with parkinsonism. **Key Words:** Risperidone—Drug-related psychosis—Atypical neuroleptics.

Drug-induced psychosis is a common complication that limits the treatment of patients with Parkinson's disease (PD).[1] Standard neuroleptics suppress hallucinations but result in unacceptable extrapyramidal symptoms.[2] Clozapine, an atypical neuroleptic purportedly with greater $5HT_{2A}$ than D_2 receptor blocking properties, provides excellent control of dopamine (DA)-related psychosis.[2] However, barriers to its use include both mandated weekly blood counts to monitor for potential agranulocytosis and reporting these results to local pharmacies before dispensing the drug. Risperidone, an atypical neuroleptic with approximately equal D_2 and $5HT_{2A}$ receptor blocking properties, is a treatment option without significant hematologic risk but one associated with a potentially higher risk of extrapyramidal side effects, including worsening parkinsonism.[3,4] The results of only small numbers of patients have been reported with the drug demonstrating limited usefulness.

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METHODS

Thirty-nine patients with parkinsonism were treated prospectively for 6 months with risperidone after developing drug-related psychosis. All patients were prescribed carbidopa–levodopa; 12 of 39 patients were taking other antiparkinsonian drugs including pramipexole (N = 4), pergolide (N = 3), ropinirole (N = 2), bromocriptine (N = 1), amantadine (N = 1), and selegiline (N = 1). Patients with presumed PD (N = 32) presented with at least three of the four cardinal manifestations of the disease, including rigidity, rest tremor, bradykinesia, and postural instability, plus an obvious and sustained benefit from either levodopa or a direct dopamine agonist. Six patients fulfilled the criteria for either possible or probable diffuse Lewy body disease (DLBD)[5] and one patient fulfilled the criteria for probable multiple system atrophy.[6] Prior to open-label risperidone treatment, a baseline Unified Parkinson's Disease Rating Scale (UPDRS)—motor scale,[7] a Hoehn and Yahr (H&Y)[8]

score, and a Mini-Mental Status Examination (MMSE)[9] were completed in most patients.

Patients who developed drug-related psychosis and who did not complete one of these baseline evaluations were unable or unwilling to return for an outpatient evaluation prior to initiating risperidone treatment. Baseline UPDRS and H&Y scores in these few patients were included if recorded previously during prior outpatient follow-up examinations within 1 month of psychosis. Risperidone therapy was initiated at 0.5 mg at bedtime and increased in 0.5-mg increments as required to suppress disruptive psychotic behavior but to no more than 3 mg per day.

Only patients with hallucinations and/or delusions that interfered with their activities of daily living, as reported by the patient or their caregiver, were treated with risperidone. Treatment response was estimated by the patient and spouse/caregiver. If there was a discrepancy between the patient and their caregiver, and the caregiver was considered an accurate historian regarding the presence or severity of psychotic symptoms or response to treatment, the caregiver's opinion was deemed more accurate. When possible, a UPDRS part III was repeated on routine follow-up examinations approximately 3 and 6 months (N = 16) later, or sooner if clinical deterioration required.

RESULTS

The cohort included 16 men and 23 women with a mean age of 74.9 ± 6.8 years (standard deviation; range, 56–88 yrs) with a mean disease duration of 10.0 ± 7.7 years. All patients had hallucinations and 16 of 39 also had delusions. Prior to risperidone treatment, the mean UPDRS part III (N = 38) was 31.46 ± 15.15. Patients had moderately advanced disease with a mean H&Y stage (N = 39) of 3.14 ± 0.7 and mean MMSE (N = 32) of 22.6 ± 6.39 (PD = 24.20 ± 4.45; non-PD = 17.0 ± 9.1).

Risperidone treatment resulted in complete or near-complete resolution of hallucinations and delusions in 23 of 39 patients and an estimated 50%–75% reduction in another four patients (Table 1). Six patients had less improvement, whereas another six patients had rapid and pronounced deterioration of parkinsonism resulting in risperidone treatment being terminated. Patients were treated with a mean risperidone dose of 1.10 mg ± 0.7 (range, 0.5–3.0 mg) for up to 26 weeks. The mean duration of treatment for 39 patients was 16.2 weeks (range, 0–26 wks). Of those 16 patients who competed the 26-week trial, mean UPDRS did not change significantly: 0 months = 31.94 ± 19.11 (range, 10–72); 3 months = 32.15 ± 19.64; 6 months = 32.59 ± 15.23.

TABLE 1. *Risperidone treatment outcome*

Response to treatment—(0–3)	
Reduction in hallucinations	
3 = (complete or near complete resolution)	23†
2 = >50%–≤75% improvement	4
1 = ≥25%–≤50%	6
0 = <25% or worsening parkinsonism*	6

* Five of six patients with no improvement or rapid worsening parkinsonism diagnosed with probable diffuse Lewy body disease.

† $p < 0.002$ (Fisher's exact test).

Response to treatment was not influenced by the MMSE prior to treatment: excellent/good = 24.62 ± 4.50; fair/poor = 23.20 ± 4.38. In 11 of 27 patients with PD with >50% improvement, the drug was discontinued because of somnolence (N = 3), nursing home transfer (N = 3), worsening parkinsonism (N = 2), palpitations (N = 1), rash (N = 1), and discontinuation of offending drug, levodopa (N = 1). Patients with PD in whom 3- and 6-month follow-up examinations were possible (N = 16) were followed until risperidone was discontinued or the patient was lost to follow up; their mean duration of treatment was 78.5 weeks (range, 26–206 wks).

Concurrent treatment with either carbidopa–levodopa or other antiparkinsonian drugs did not change significantly during the 6 months of the study. There was no increase in dopamine agonist therapy. As a group, a small but statistically insignificant increase in carbidopa–levodopa levels was necessary to maintain satisfactory motor functions (0 months = 616.7 ± 428.3 mg per day; 6 months = 653.3 ± 433.0 mg per day). Additional psychoactive drugs were not added during the 6 months of observation.

DISCUSSION

Atypical neuroleptics are effective antipsychotic drugs with low extrapyramidal side effects.[10] Although clozapine is considered the standard atypical neuroleptic, other drugs, including risperidone, have similar therapeutic characteristics[11,12] in that they relieve hallucinations with reduced extrapyramidalism when compared with standard neuroleptics, in part by their ability to preferentially antagonize $5HT_{2A}$ rather than D_2 receptors.[13,14] Because risperidone use does not require weekly laboratory testing, it became the first atypical neuroleptic alternative to clozapine for treating dopamine-related psychosis in patients with PD.

Early reports of risperidone use in patients with PD were promising; hallucinations resolved without significant worsening of parkinsonian features. Meco et al.[15] initially studied six patients with PD resulting in "encouraging" results using an average dose of 0.67 mg per day. Meco et al.[16] later noted significant improvement of

levodopa-induced psychosis in 10 patients with the average dose of 0.73 mg per day, although treatment was halted in two patients because of worsening parkinsonism. Damecour and Turcotte[17] and Geizer and Ancill[18] each reported one patient with improved psychosis without increasing parkinsonism. Workman et al. did not observe worsening extrapyramidal symptoms in nine patients with PD who were treated successfully with risperidone during a psychiatric hospitalization, but they also did not provide a post-discharge neurologic status. Similar to our patients, their risperidone-treated patients did not require altering antiparkinsonian medications. Hallucinations in patients with DLBD may also be risperidone-responsive without worsening extrapyramidal symptoms.[19]

Subsequent reports have failed to provide enthusiasm for risperidone use in patients with PD. Ford et al.,[3] after treating six patients with PD with an average daily dose of 1.5 mg, concluded that risperidone was not a satisfactory substitute for clozapine. Although parkinsonism deteriorated in all patients, the UPDRS change was steep in only one patient. Further, despite the advanced disease of their cohort, the UPDRS decline averaged less than 5 points. Rich et al.[4] also evaluated only six patients. Hallucinations in one patient resolved with no extrapyramidal worsening. Of the patients with increased parkinsonism, two patients had probable DLBD and two patients were prescribed 2 mg risperidone per day. The remaining patient declined gradually from a H&Y stage 4 to stage 5 on risperidone over 4 months, a deterioration not clearly from risperidone treatment; there was no indication the drug was stopped. Gil et al.,[20] using risperidone doses of 0.5–2.0 mg per day, reported a 12%–20% increase in UPDRS scores in six patients with PD; hallucinations resolved in five patients.

Risperidone-induced extrapyramidal complications have also been reported in other patient populations. Rosebush and Mazurek,[21] using average risperidone doses between 3 and 4 mg per day in neuroleptic-naive psychiatric patients, observed a rate of parkinsonism comparable to their haloperidol-treated cohort. However, their dose schedule is nearly triple that used in our psychotic patients with PD.

Opponents of risperidone use in PD also support their position with radioligand evidence that the drug has D_2 receptor blocking properties quantitatively similar to that of the standard neuroleptics. Indeed, positron emission tomography and I-123 iodobenzamine SPECT measure risperidone striatal D_2 receptor binding at 60%–90% when administered in therapeutic doses to patients with schizophrenia.[22,23] However, in normal volunteers given 1 mg risperidone, D_2 receptor binding falls to 55%–64%, an indication that risperidone D_2 occupancy is dose-dependent.[12] Therefore, low-dose risperidone (0.5–1.5 mg per day), such as used in all but three of our patients, may be therapeutic in patients with PD without subjecting them to an undue risk of increasing parkinsonism. Indeed, a chart review of the 16 patients with PD who completed the intended 6-month period of observation found continuing control of hallucinations for over 1.5 years. Further, in our experience, a marked decline in motor functions occurring suddenly after initiating low-dose risperidone treatment suggests the alternative diagnosis of DLBD. That other reports of risperidone use in patients with PD are less sanguine may be a reflection of the small numbers of studied patients or that in some patients the drug was discontinued as a result of worsening of parkinsonism unrelated to risperidone use.

Our results should not be construed as an endorsement of risperidone as initial treatment for drug-induced psychosis in patients with PD, in part because we did not formally rate the severity of psychosis or attempt to quantitate the impact to treatment success of our patients' quality of life. We did demonstrate that in psychotic patients with PD, low-dose risperidone may be beneficial and well-tolerated. Later iterations of the atypical antipsychotics, such as olanzapine and quetiapine, are also effective treatment and may have fewer extrapyramidal complications.

REFERENCES

1. Cummings JL. Neuropsychiatric complications of drug treatment of Parkinson's disease. In: Huber SJ, Cummings JL, eds. *Parkinson's Disease: Neurobehavioural Aspects.* New York, NY: Oxford Press, 1992:313–327.
2. Casey DE. The relationship of pharmacology to side effects. *J Clin Psychiatry* 1997;58(suppl 10):55–62.
3. Ford B, Lynch T, Greene P. Risperidone in Parkinson's disease. *Lancet* 1994;344:681.
4. Rich SS, Friedman JH, Ott BR. Risperidone versus clozapine in the treatment of psychosis in six patients with Parkinson's disease and other akinetic-rigid syndromes. *J Clin Psychiatry* 1995;56:556–559.
5. McKeith IG, Perry RH, Fairbairn AF, Jabeen S, Perry EK. Operational criteria for senile dementia of Lewy body type (SDLT). *Psychol Med* 1992;22:911–922.
6. Albanese A, Colosimo C, Bentivoglio AR, et al. Multiple system atrophy presenting as parkinsonism: clinical features and diagnostic criteria. *J Neurol Neurosurg Psychiatry* 1995;59:144–151.
7. Fahn S, Elton RL, the UPDRS Development Committee. Unified Parkinson Disease Rating Scale. In: Fahn S, Marsden CD, Calne D, et al, eds. *Recent Developments in Parkinson's Disease,* vol 2. Florham Park, NJ: Macmillan, 1987:153–163.
8. Hoehn MM, Yahr M. Parkinsonism: onset, progression, and mortality. *Neurology* 1967;17:427–442.
9. Folstein MF, Folstein SE, McHugh PR. 'Mini-mental state.' A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975;12:189–198.
10. Balldessarini RJ, Frankenbutg FR. Clozapine: a novel antipsychotic agent. *N Engl J Med* 1991;324:746–754.

11. Borison RL, Pathiraja AP, Diamond BI, Meibach RC. *Psychopharmacol Bull* 1992;28:213–218.
12. Chouinard G, Jones B, Remington G, et al. A Canadian multicenter placebo-controlled study of fixed doses of risperidone and haloperidol in the treatment of chronic schizophrenic patients. *J Clin Psychopharmacol* 1993;13:25–40.
13. Meltzer HY. Role of serotonin in the action of atypical antipsychotic drugs. *Clin Neurosci* 1995;3:64–75.
14. Bruggeman R, Westerink BH, Timmerman W. Effects of risperidone, clozapine and haloperidol on extracellular recordings of substantia nigra reticulata neurons of the rat brain. *Eur J Pharmacol* 1997;324:49–56.
15. Meco G, Alessandria A, Bonifti V, Giustini P. Risperidone for hallucinations in levodopa-treated Parkinson's disease patients. *Lancet* 1994;343:1370–1371.
16. Meco G, Alessandria A, Giustini P, Bonifti V. Risperidone in levodopa-induced psychosis in advanced Parkinson's disease: an open-label, long-term study. *Mov Disord* 1997;12:610–613.
17. Damecour CL, Turcotte J-R. Therapeutic dilemma: psychosis and Parkinson's disease. *Can J Psychiatry* 1995;40:640–641.
18. Geizer M, Ancill RJ. Combination of risperidone and donepezil in Lewy body dementia. *Can J Psychiatry* 1998;43:421–422.
19. Allen RL, Walker Z, D'Ath PJ, Ceduna CL. Risperidone for psychotic and behavioural symptoms in Lewy body disease. *Lancet* 1995;346:185.
20. Gil A, Calopa M, Pellise A, Jato M, Peres J. Risperidone treatment of psychotic symptoms in Parkinson's disease. *Mov Disord* 1996; 11(suppl 1):169.
21. Rosebush PI, Mazurek MF. Neurologic side effects in neuroleptic-naive patients treated with haloperidol or risperidone. *Neurology* 1999;52:782–785.
22. Farde L, Nyberg S, Oxenstierna G, Nakashima Y, Halldin C, Ericksson B. Positron tomography studies on D_2 and 5-HT_2 receptor binding in risperidone-treated schizophrenic patients. *J Clin Psychpharmacol* 15(suppl 1):19S–23S.
23. Knable MB, Heinz A, Raedler T, Weinberger DR. Extrapyramidal side effects with risperidone and haloperidol at comparable D2 receptor occupancy levels. *Psychiatry Research Neuroimaging Section* 1997;75:91–101.