

Withdrawal-Emergent Dyskinesia in a Patient on Risperidone Undergoing Dosage Reduction

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A 23-year-old, white male with a history of paranoid schizophrenia developed a withdrawal-emergent dyskinesia during a dose reduction of risperidone. The implications of this with regard to future risk of tardive dyskinesia (TD) and the potential association of risperidone with TD are discussed.

KEY WORDS: Risperidone; withdrawal-emergent; tardive dyskinesia.

INTRODUCTION

Risperidone represents a prototype of a new class of antipsychotics, the serotonin-dopamine antagonists (SDAs), of which clozapine was the forerunner. At the time of its marketing and as substantiated to varying degrees by several studies thereafter, it was claimed to possess several distinguishing characteristics from conventional neuroleptics. It was reported to be more efficacious in ameliorating negative symptomatology than the traditional neuroleptics (1). Most studies examining the overall efficacy of this medication have concluded that it is at least as effective as, if not more so than, the conventional drugs (2,3). In addition, due to its low D2/5HT2 binding ratio, it was also reported to cause a lower incidence and severity of extrapyramidal adverse effects (4,5). However, data on the long-term adverse effect profile are sparse and the issue of tardive dyskinesia (TD) and the related withdrawal-emergent dyskinesia (WE-D) have not been adequately addressed in the literature.

Tardive dyskinesia (TD) is probably the most serious adverse effect of long-term antipsychotic therapy with no current strategy for primary prevention (6). Similar dyskinetic movements observed dur-

ing dose reduction of antipsychotics in the absence of documented TD have been referred to as withdrawal-emergent dyskinesia (WE-D) (6,7). We report a case of WE-D occurring in a patient undergoing dose reduction of risperidone. To our knowledge this is the first such case to be reported.

CASE REPORT

J.E. is a 23-year-old, single, white male with a 3-year history of paranoid schizophrenia. His index psychotic episode at age 20, characterized by delusions, auditory hallucinations, and extreme thought disorganization, occurred during his first week of boot camp training and had been preceded by several months of negative symptomatology including social withdrawal, lack of motivation, and affective flattening. His first hospitalization lasted two months, during which he was treated with haloperidol, 25 mg po bid, benztropine, 2 mg po qhs, and lorazepam prn. Following this he was transferred to another facility, where his stay lasted a week, during which time the dose of haloperidol was reduced to 2 mg po bid. At this time he was noticed to be experiencing severe extrapyramidal symptoms (EPS) but no evidence of TD was observed.

The patient discontinued all medications less than a month following discharge. He remained asymptomatic for the next 8 months, after which he experienced his second psychotic episode resulting in

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another 2-month-long hospital stay during which he was initially tried on escalating doses of perphenazine (up to 40 mg/day). When no response was seen he was then switched to haloperidol, 10 mg po bid, with good results. Again, he discontinued all medications in a month following discharge. He remained asymptomatic for the next year and a half before experiencing his third psychotic episode at age 22 in August 1995.

Once again the patient was hospitalized and this time started on risperidone, 1 mg po bid, with doses gradually escalating, by 1 mg/day every 4–5 days. A maximal dose of 8 mg/day was used, which adequately controlled the acute psychosis. However, the patient experienced an unusually distressful degree of neck and back stiffness, was moderately rigid, and constantly complained of an ache in his scalp in a “cap”-like distribution. Benztropine was used at increased doses up to 6 mg/day in an attempt to ameliorate these symptoms but relief was only partial and was accompanied by severe anticholinergic side effects including dry mouth, blurred vision, and urinary hesitancy. Two strategies were employed sequentially to manage this situation. First, the dose of risperidone was gradually reduced to 6 mg/day, the rate of reduction being 1 mg every 4–5 days. This provided partial relief from the EPS. Second, benztropine was discontinued and amantadine was started at a dose of 100 mg po bid, increasing to a total of 300 mg/day within a week. This further improved the EPS and provided further relief from anticholinergic effects. The patient was discharged on the above medications at the stated doses. At no time during the inpatient stay were any movements indicative of TD noted.

During the following several weeks the patient was seen weekly at the outpatient clinic. Due to persistent EPS the dose of risperidone was further decreased to 5 mg/day. Soon he began to complain of persistent depressive symptoms and was rehospitalized for treatment of depression 3 months after the onset of the third psychotic episode.

In the course of this hospitalization (he is now age 23) he was started on increasing doses of venlafaxine, up to 250 mg/day, with good results. In addition, the dose of risperidone was further dropped to 4 mg/day, and amantadine reduced to 100 mg bid. Within 4 days of the reduction in the dose of risperidone the patient was noted to develop a thick tongue, which frequently protruded out of his mouth and was associated with significant puckering and smacking of

his lips. These movements remained fairly severe for approximately a week and then gradually decreased in frequency and severity. They were clearly exacerbated in anxiety-provoking situations, though the patient did not seem to be alarmed by them. A tongue tremor was also noted. Benztropine was restarted to treat EPS and the dose increased to 3 mg/day coincident with the waning of the buccolingual movements. The patient was also started on clonazepam, 0.5 mg po bid, to treat anxiety and restlessness. At the time of discharge the patient still had occasional tongue protrusion with rare lip-smacking.

DISCUSSION

The broad differential diagnosis of the hyperkinetic buccolingual movements described in the above case includes an antipsychotic-induced dyskinesia, dyskinesia induced by other drugs (e.g., levodopa, tricyclics, amphetamines), dyskinesia induced by other illnesses (e.g., hypothyroidism, SLE), hereditary conditions (Huntington's chorea, Wilson's disease), idiopathic conditions (e.g., Tourette's syndrome), and miscellaneous conditions (e.g., dental problems) (11). However, the nature of the phenomenology, associated clinical circumstances, and temporal profile and absence of other probable etiologies clearly implicated the antipsychotic risperidone in the causation of these movements. The fact that the phenomenon occurred in the context of concurrent administration of amantadine and venlafaxine did not weaken our case. Though amantadine augments dopamine activity and could theoretically lower the threshold for such a syndrome, no amantadine-related dyskinesias have been reported based on review of the existing literature by computer search. It would not be expected for venlafaxine to affect the threshold for a dyskinesia. Tardive dyskinesia has often been observed to develop after long-term exposure to conventional neuroleptics (5), though most studies thus far have failed to establish a definite relationship between the occurrence of TD and the specific neuroleptic dose and/or duration of treatment (12,13). Other risk factors include old age, female sex, affective disorders, and possibly organic brain disease (7,14,15). Given our patient's treatment, epidemiological and disorder profile, TD is unlikely. His exposure to neuroleptics was sporadic (total of 3 to 4 months over a period of 3 years) and was certainly not long term. To our knowledge there has

been only once case report of TD developing in a patient while on risperidone (8). Even in that case, a long history of conventional neuroleptic use precluded the clear correlation of TD and current risperidone use.

Withdrawal-emergent dyskinesia refers to the development of abnormal movements during antipsychotic dose reduction in patients who do not already have a diagnosis of persistent TD (6). Both past and recent literature on the subject is sparse. Earlier investigators have attempted to characterize the phenomenon and explain its significance (10,14). A more recent study (6) found statistically significant differences between patients with TD/WE-D and those without and significant similarities between patients with persistent TD and WE-D. These investigators hypothesized that the presence of WE-D may predict a vulnerability to the development of persistent TD and may, in fact, represent an early manifestation of TD. This is in contrast to the previous belief that WE-D typically remitted spontaneously in a few weeks or months (5). A caveat in the current data involves differentiation of new-onset WE-D from unmasking of persistent TD (covert dyskinesia). This appears to be inapplicable to the case in question since our patient never showed evidence of TD even during long medication-free intervals.

We are unaware of previous reports of cases where risperidone was clearly implicated in the development of WE-D. If we are to assume that WE-D and TD actually exist on a continuum of severity, this case raises an interesting paradox given the fact that risperidone has actually been shown to possess antidyskinetic properties (9). The Canadian Multicenter Risperidone Study confirmed that risperidone possessed significant antidyskinetic properties in patients with at least moderately severe TD and that doses of 6 mg/day were effective for the buccolingual movement (BLM) syndrome, a form of TD that has a greater tendency to be irreversible.

Several features are noteworthy in this case. First, our patient was exceptionally sensitive to neuroleptics, suffering from severe EPS even on low doses of traditional neuroleptics and on recommended doses of risperidone (2). Previous studies indicate that the development of EPS may be a powerful predictor of development of TD (14,16), putting our patient at risk for persistent TD. Second, the fact that administration of bztropine to treat EPS did not exacerbate the WE-D lends support to the current thinking that the previously supposed

positive association of anticholinergic drugs and TD may in fact be spurious (7,17). Third, benzodiazepines have been studied as possible treatment options for TD (18,19). Our patient was receiving clonazepam for treatment of anxiety at the time of development of WE-D. This, however, may not be conclusive since studies have usually cited the use of higher doses.

Some questions remain unanswered. It is unclear why a similar WE-D did not appear during the initial dose reductions from 8 to 6 mg/day and then again from 6 to 5 mg/day. One possible explanation could be the presence of severe depressive symptoms during the latter dose reduction (5 to 4 mg/day), since affective illness has been cited as a risk factor for TD (7,14,15). The greatest dilemma now, however, is regarding the next step in management. This involves a choice between continuing on risperidone at the same or a lower dose (assuming that the psychosis continues in remission as it is now) or switching over to clozapine and dealing with its attendant management issues and risks.

In summary, we have presented a case of WE-D developing during dose reduction of risperidone and raised questions regarding its role in causing and/or treating TD. Further long-term studies are required before firm conclusions can be drawn.

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