Clozapine Withdrawal Resulting in Delirium With Psychosis: A Report of Three Cases

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Background: Withdrawal symptoms for typical antipsychotics are generally mild, self-limited and do not include development of psychotic symptoms. In contrast, withdrawal symptoms for clozapine can be severe with rapid onset of agitation, abnormal movements, and psychotic symptoms. Different pathophysiologic etiologies have been suggested for these severe symptoms, including dopaminergic supersensitivity and rebound.

Method: Three case reports of clozapine withdrawal symptoms are presented. A review of previous case reports and discussion of the etiology of withdrawal symptoms of typical antipsychotics and clozapine are provided.

Results: These three patients developed delirium with psychotic symptoms that resolved rapidly and completely upon resumption of low doses of clozapine.

Conclusion: The severe agitation and psychotic symptoms after clozapine withdrawal in these three patients were due to delirium, perhaps the result of central cholinergic rebound. The withdrawal symptoms and delirium resolved rapidly with resumption of low doses of clozapine. Severe withdrawal symptoms can probably be avoided by slowly tapering clozapine and/or simultaneously substituting another psychotropic with high anticholinergic activity, such as thioridazine.

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Symptoms associated with the withdrawal of antipsychotic medications have been recognized since their earliest use.[1–3] These symptoms of nausea, vomiting, marked diaphoresis, increased sebaceous secretion, restlessness, and general physical complaints occur in varying combinations, peak within a few days, and resolve without treatment in about 1 week. Extrapyramidal symptoms also sometimes occur but are most likely related to the simultaneous withdrawal of antiparkinson agents.[3] Psychotic symptoms are not part of the withdrawal reactions.[4,5]

Withdrawal symptoms for clozapine can differ from those of typical antipsychotics. Symptoms, in addition to those above, include rapid onset of severe agitation, abnormal movements, and psychotic symptoms.[6–12]

We present the cases of three patients who, within a few days of stopping clozapine, developed agitated delirium with psychosis that responded rapidly to the resumption of clozapine. Two who had histories of tardive dyskinesia (TD) also developed severe choreoathetoid movements, which also resolved after clozapine was resumed.

CASE REPORTS

Case 1

Mr. A, a 46-year-old white man with a 27-year history of refractory schizoaffective disorder, had been an inpatient for 17 years. He had moderately severe TD and parkinsonism and delusions of reference and control. He attended to all his activities of daily living, went on hospital grounds unsupervised, and worked in a workshop. He had been stable for several months on a regimen of clozapine (300 mg/day; serum clozapine level = 105 ng/mL, serum norclozapine level = 56 ng/mL), lithium (2700 mg/day; 1.5–1.7 mEq/L), and divalproex sodium (1500 mg/day; 70–80 μg/mL). He had received clozapine for over 1 year at doses up to 600 mg/day. TD and parkinsonism improved, but psychotic symptoms had not, so it was decided to withdraw clozapine and resume a standard antipsychotic.

Clozapine was weaned over 2 weeks from a dose of 300 mg/day—initially by 100 mg/day and then by 50 mg/day every 3 to 4 days. Lithium and divalproex sodium

were continued at the same doses. Another antipsychotic was not immediately restarted.

Twenty-four hours after the last dose of clozapine, Mr. A became confused, disorganized in speech, and unable to get dressed or eat without assistance. The following morning he was agitated, diaphoretic, incontinent of urine, and pacing constantly. Over the next few hours, continuous, slow, choreoathetoid movements developed first in his hands and fingers, and then in neck, trunk, and all limbs, along with continuous, severe facial grimacing. When standing, he gave the impression of dancing because of the chorea of his legs and the slow serpentine waving of his arms. While he was lying down, all the movements continued. At times his legs flexed slowly at the waist, up over his trunk, so that his feet were by his head. He was profusely diaphoretic, oriented only to name, and spoke in complete word salad. He had moderate tonus in all extremities, but no rigidity across any joints. Deep tendon reflexes were hypotonic, and there was no clonus. He developed visual hallucinations, picking at things in the air, and became assaultive when he no longer recognized staff.

Benztropine 2 mg i.m. was given after blood studies were obtained. Within 30 minutes, choreoathetoid movements, agitation, and diaphoresis markedly decreased, and speech became coherent. Three hours after the injection, though, severe choreoathetoid movements, diaphoresis, and agitation had returned. A second 2-mg injection of benztropine produced similar improvement.

Laboratory results revealed a white blood cell (WBC) count of 23,000/cu mm and a creatinine phosphokinase (CK) level of 581 IU/L (normal, 25–175). Serum lithium (1.5 mEq/L) and valproate (81 μg/mL) levels were unchanged. Other values were within normal limits. Vital signs and temperature were stable.

Symptoms began again 2 hours after the second injection of benztropine, so clozapine 50 mg p.o. was given. One hour later, choreoathetoid movements, diaphoresis, and agitation began to decrease and stopped completely within 10 minutes. The patient slept throughout the night.

The following morning, Mr. A was pleasant, oriented, coherent in speech, and cooperative. Mild disorganization and ataxia resolved over the next day, and he returned to his prewithdrawal level of function. Clozapine was increased to 150 mg/day over 4 days. Divalproex sodium and lithium were continued unchanged. CK and WBC values returned to normal over the next week. No fever or infection ever developed. The results of a chest x-ray were normal, and the findings for urine and blood culture tests were negative.

Case 2

Mr. B, a 63-year-old white male outpatient, had a 20-year history of chronic paranoid schizophrenia. He had responded to typical antipsychotics but developed TD and laryngeal dystonia, which produced grunting with breathing. He was treated with clozapine because of the dyskinetic movements, all of which resolved.

He had been taking clozapine for 1 year (250 mg/day, serum level = 220 ng/mL), when he ran out of medication. Two days after his last dose (200 mg h.s.), he called to complain of disturbing auditory hallucinations that were as severe as when he first became ill. At that time, he had been arrested for driving recklessly, trying to get away from the voices.

Mr. B was seen the following day. He was wide-eyed, agitated, and grunting considerably. Even though it was a cold day, he was profusely diaphoretic and soaked with sweat. He was confused, disoriented for time, unable to focus his attention, and had difficulty in speaking. He had extreme choreoathetoid movements and was writhing continuously, making it difficult for him to remain in a chair. He was given 50 mg of clozapine. Within 1 hour, agitation, confusion, choreoathetoid movements, diaphoresis, and auditory hallucinations dramatically decreased. Clozapine was gradually increased to 250 mg/day over 3 days, during which time all symptoms resolved, and he has continued to do well.

Case 3

Mr. C, a 38-year-old white man with a 25-year history of refractory undifferentiated schizophrenia, had been an inpatient for 18 years. Residual symptoms were negative symptoms with no hallucinations. He attended to all his activities of daily living, went on hospital grounds unsupervised, and worked in a workshop.

He had been stable on clozapine 250 mg/day (serum level = 1000 ng/mL), lithium 1500 mg/day (1.2 mEq/L), and fluoxetine 40 mg/day for 18 months. A routine electrocardiogram (ECG) revealed a new incomplete right bundle-branch block and anterolateral T wave changes. Clozapine was stopped immediately because of concern about the conduction abnormalities. Fluoxetine and lithium were continued unchanged.

Over the next 5 days, Mr. C became agitated, intermittently disoriented to place, disorganized, and unable to leave the unit. He developed decreased attention and disturbed sleep. Nausea, vomiting, and nasal congestion were present for 2 days. Over the next few days, he became completely disoriented to time and place, incomprehensible in speech, and unable to follow verbal commands. He was unable to shower, eat, or get dressed by himself and became incontinent of feces. At times he was assaultive. During brief lucid periods, he reported fear of severe auditory hallucinations, delusions about UFOs, and bizarre visual hallucinations of God.

His deteriorated condition continued for 3 weeks. The ECG abnormalities resolved, and clozapine was restarted at 25 mg b.i.d. The first night he slept well, and the following day the disorientation, disorganization, and agitation

were much improved. Auditory and visual hallucinations resolved over 3 days. Clozapine was titrated to 100 mg b.i.d. over a week, and he returned to his prewithdrawal level of function.

Electrocardiogram conduction abnormalities reoccurred, and clozapine was again stopped abruptly, but this time risperidone was immediately substituted. An identical clinical picture developed over several days, though, including auditory and visual hallucinations, disturbed sleep, disorientation, confusion, and inability to care for himself. Steady deterioration continued despite the use of risperidone (3 mg b.i.d.). Three weeks after clozapine had been stopped, risperidone was stopped, and clozapine was restarted (25 mg b.i.d.). There was rapid improvement in agitation, confusion, and sleep after the first dose, and a return to prewithdrawal function over a week, while clozapine was titrated to 100 mg b.i.d.

DISCUSSION

Surveys and controlled studies have found that withdrawal symptoms of typical antipsychotics are relatively common, mild, and self-limited. In contrast, descriptions of clozapine withdrawal symptoms, although limited to case reports, have stressed their severity.

Each of these patients developed extremely severe symptoms and a reduced level of consciousness, which initially fluctuated and eventually became constant, with corresponding increased agitation. This is the hallmark of delirium.[13] The four patients described by Simpson and colleagues also had developed marked clouding of consciousness.[6,7] No other published report has mentioned the level of consciousness.

Some authors have suggested that the severe psychotic symptoms following clozapine withdrawal are due to a supersensitivity psychosis that develops because of clozapine-induced dopamine receptor hypersensitivity.[8,10] Others have suggested that this explanation alone would not account for the rapid onset of symptoms and that some other process must be involved.[9,11]

Another explanation is that the agitation and hallucinations result from delirium. Each patient developed symptoms meeting criteria for substance withdrawal delirium (DSM-IV)—change in cognition (disorientation, disorganized speech, apraxia) and reduced level of consciousness[14]—that developed rapidly after clozapine withdrawal and fluctuated throughout the day.

Psychotic relapse in schizophrenic patients following withdrawal of typical antipsychotics usually occurs over a period of weeks to months and is generally preceded by nonpsychotic prodromal changes.[5,15] The hallucinations and delusions described in clozapine withdrawal could be due to the perceptual disturbance of delirium. Patients 1 and 3 had visual hallucinations, which they had never had previously and which resolved with resolution of the delirium after clozapine was restarted. Additionally, an electroencephalogram obtained on Patient 1 during the symptomatic period demonstrated diffuse, bilateral slow rhythm of 5–7 Hz, which is consistent with delirium, rather than a normal rhythm of 8–12 Hz.

Pathophysiology

Symptoms following antipsychotic withdrawal are thought to result from withdrawal of the anticholinergic effect of the antipsychotic, which leads to rebound increased cholinergic activity.[3] Peripheral cholinergic rebound produces nausea, vomiting, diaphoresis, and rhinitis. Mild central cholinergic rebound produces restlessness and insomnia.[3,18] Similar symptoms occur after withdrawal of any psychotropic having anticholinergic activity, and the more potent the anticholinergic activity, the more likely symptoms are to occur.[16–18]

Severe clozapine withdrawal symptoms could be caused by greater central cholinergic rebound, due in part to clozapine's extremely potent antimuscarinic activity.[19] Symptoms of central cholinergic rebound would be similar to those of a centrally acting cholinergic agonist—parkinsonian effects, ataxia, and hypertonia. These theoretically result from activation of muscarinic receptors in the basal ganglia.[20,21] Central cholinergic toxicity produces irritability, restlessness, ataxia, delirium, and hallucinations.[22]

Several findings suggest that increased cholinergic activity contributed to these withdrawal symptoms. All three patients had some peripheral cholinergic symptoms (diaphoresis, nausea, vomiting, rhinitis). Patient 1 displayed all the symptoms of central cholinergic toxicity (ataxia, hypertonia, restlessness, hallucinations, delirium), all of which improved with benztropine. Patient 3 developed symptoms despite immediate substitution of risperidone. Risperidone has no antimuscarinic activity to block the cholinergic rebound. Risperidone does block dopamine (D_1 and D_2) and 5-HT_2 receptors, so that withdrawal symptoms were less likely to be related to dopaminergic or 5-HT_2 rebound.[23]

Increased cholinergic activity could have contributed to choreoathetoid movements, since the movements improved with benztropine. Choreoathetoid movements occurred only in the two patients with histories of severe TD, which suggests involvement of additional receptor effects.

Control of motor activity involves interaction of dopaminergic, cholinergic, and GABAergic neurons.[24] Huntington's disease involves the loss of cholinergic and GABAergic neurons in the striatum, but the exact mechanism producing chorea is not known.[24] The etiology of TD is also unknown, although there is evidence for alterations of dopamine and other receptors.[25] Clozapine affects all of these receptors, but any theory for the etiology of the withdrawal choreoathetoid movements is speculative.

Patients 1 and 3 were receiving other medications (lithium, divalproex sodium, fluoxetine), which may have contributed to the withdrawal symptoms. It is unlikely that these agents were the primary cause, though, since they were continued unchanged, and all symptoms resolved rapidly after resumption of clozapine.

Treatment

Low doses of clozapine (25–50 mg) resulted in rapid improvement of the withdrawal symptoms, indicating that large initial doses are unnecessary. A prolonged taper is the preferred method for discontinuing clozapine, and a longer taper period may have prevented the symptoms in Patient 1.

When clozapine is stopped abruptly (e.g., for agranulocytosis), substituting a psychotropic with high anticholinergic activity (e.g., thioridazine) may prevent withdrawal symptoms. Anticholinergics have been used to treat the withdrawal effects of other psychotropics,[16] and trihexyphenidyl has been used to treat gastrointestinal symptoms associated with abrupt clozapine withdrawal.[26]

We have since withdrawn clozapine from six patients. Two withdrawn abruptly from 600 mg/day were immediately started on thioridazine (50–100 mg p.o. b.i.d.). Four were weaned over 4 to 8 weeks, and thioridazine was added during the last 2 weeks of clozapine treatment. Five of the six were then treated with risperidone. Risperidone was added to thioridazine, which was tapered and stopped over 2 weeks. None of the six developed any withdrawal symptoms.

There have been no controlled assessments of clozapine withdrawal, so the incidence of severe symptoms is unknown and may be rare. Because of the potential severity of symptoms, though, we now routinely add thioridazine when discontinuing clozapine and before substituting another antipsychotic.

Drug names: benztropine (Cogentin and others), clozapine (Clozaril), divalproex sodium (Depakote), fluoxetine (Prozac), risperidone (Risperdal), thioridazine (Mellaril and others), trihexyphenidyl (Artane and others).

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