Risks and benefits of rapid clozapine titration

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Abstract

Clozapine is often considered the gold standard for the treatment of schizophrenia. Clinical guidelines suggest a gradual titration over 2 weeks to reduce the risks of adverse events such as seizures, hypotension, agranulocytosis, and myocarditis. The slow titration often delays time to therapeutic response. This raises the question of whether, in some patients, it may be safe to use a more rapid clozapine titration. The following case illustrates the potential risks associated with the use of multiple antipsychotics and rapid clozapine titration. We present the case of a young man with schizophrenia who developed life threatening neuroleptic malignant syndrome (NMS) during rapid clozapine titration and treatment with multiple antipsychotics. We were unable to find another case in the literature of NMS associated with rapid clozapine titration. This case is meant to urge clinicians to carefully evaluate the risks and benefits of rapid clozapine titration, and to encourage researchers to further evaluate the safety of rapid clozapine titration. Rapid clozapine titration has implications for decreasing health care costs associated with prolonged hospitalizations, and decreasing the emotional suffering associated with uncontrolled symptoms of psychosis. Clozapine is considered the most effective antipsychotic available thus efforts should focus on developing strategies that would allow for safest and most efficient use of clozapine to encourage its utilization for treatment resistance schizophrenia.

Introduction

Schizophrenia is a disorder characterized by delusions, hallucinations, disorganized speech, disorganized behavior, and/or negative symptoms. There is an estimated worldwide prevalence of 1%. The disease course may range from recovery of functioning to complete disability.[1] There are many patients, who fail to achieve adequate symptom reduction after multiple trials of neuroleptic medications. These treatment resistant patients should be provided with a trial of clozapine, which is often viewed as the gold standard for the treatment of schizophrenia.[2]

Clozapine is considered to be the most effective antipsychotic drug.[3] Clozapine is a serotonin-dopamine antagonist with a complex pharmacologic profile. It has been labeled the gold standard in treatment for schizophrenia, when other medications have failed.[4] Clozapine is thought to cause fewer extrapyramidal side effects, may reduce tardive dyskinesia severity, and some studies suggest it is protective against suicide.[5,6] Clinical guidelines suggest a gradual titration of clozapine over two weeks to reduce the risks of adverse events such as seizures, hypotension, agranulocytosis, and myocarditis.[7]

Unfortunately, this slow titration often delays time to therapeutic response.[8] The standard titration starts with clozapine 25 mg daily given in 2 divided doses, and then clozapine is increased by 25-50 mg per day each day until desired efficacy. The typical maintenance dose of clozapine is 300-450 mg daily. This gradual titration may also necessitate the concomitant administration of multiple antipsychotics to control aggressive or assaultive behaviors. This raises the question of whether, in some patients, it may be safe to use a more rapid clozapine titration. There is limited data to support the practice of a more rapid clozapine titration.[9,10]

There is no consistent definition of *rapid* clozapine titration or evidence to support which patients may be safe for a rapid titration. There is also limited evidence to support rapid titration of clozapine. A recent naturalistic cohort study of rapid clozapine titration was shown to be safe and effective.[9] This study used a rapid titration defined as a starting dose of 25 mg and increased by 25-50 mg every 6 hours, no more than 100 mg daily, until control of symptoms. There were no major complications during this titration, and average titration took about 4 days. This study was limited by a small sample size. It does raise the question of whether select patients may tolerate and benefit from a rapid titration.

The following case illustrates the potential risks associated with the use of multiple antipsychotics and rapid clozapine titration. We present the case of a young man with schizophrenia who developed life threatening neuroleptic malignant syndrome (NMS) during rapid clozapine titration. We were unable to find another case in the literature of NMS associated with rapid clozapine titration. This case is meant to urge clinicians to carefully evaluate the risks and benefits of rapid clozapine titration, and to encourage researchers to further evaluate the safety of rapid clozapine titration.

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Case Report

Our patient is a 21-year-old African-American college student with a three-year history of schizophrenia and methamphetamine use disorder. He was admitted to a residential facility on 13 December 2014 with command auditory hallucinations, delusions, insomnia, and disorganization. He was guarded, aggressive, and had homicidal ideation towards his physician, staff and mother.

Medications on admission included duloxetine 60 mg daily, oxcarbazepine 600 mg twice daily, aripiprazole 400 mg IM monthly, and lorazepam 2 mg PRN. He was not continued on any home medications upon admission. He was titrated up to risperidone 6 mg daily in combination with chlorpromazine 200 mg daily. During the first week he required multiple emergency doses of haloperidol 10 mg, diphenhydramine 50 mg, and lorazepam 2 mg for aggression. There was minimal improvement after an approximately three week trial of risperidone and chlorpromazine. Rapid titration of clozapine was initiated on 30 December, started at 25 mg and increased to 175 mg by 6 January 2015. Divalproex sodium was started on 6 January. He continued to

episodically require seclusion and restraints. On 8 January 2015, clozapine was at 300 mg daily. Psychotic symptoms improved, however he rapidly developed rigidity, lethargy, and disorientation. He was febrile to 106°F, pulse was 120 beats/min, and CK level was 2733 U/L. He was transferred to a medical unit with the presumed diagnosis of neuroleptic malignant syndrome. He was subsequently treated symptomatically with lorazepam and acetaminophen, stabilized, and returned to residential facility.

Discussion and Conclusions

This case illustrates the life threatening risks associated with rapid clozapine titration and treatment with multiple antipsychotics. The National Institute of Mental Health founded Clinical Antipsychotic Trials for Interventions Effectiveness sought to evaluate the comparative effectiveness of antipsychotic drugs. It showed that in patients with schizophrenia who did not achieve adequate symptom reduction with an atypical antipsychotic, switching to clozapine was more effective than switching to an alternative atypical antipsychotic.[3] Clozapine requires a gradual dose titration to decrease the potential for life threatening side effects of hypotension, seizures, agranulocytosis, myocarditis, and neuroleptic malignant syndrome. However, gradual titration delays the time to adequate treatment of psychosis and agitation, and often necessitates the risky use of multiple antipsychotics and prolonged hospitalization.[8]

The use of a rapid clozapine titration should only be considered on an individual basis given each patient's unique symptoms. It remains unclear if this patient's adverse reaction was due to rapid clozapine titration. The neuroleptic malignant syndrome may have been secondary to treatment with multiple antipsychotics, interactions between medications, a combination of these factors, or simply initiation of clozapine. The incidence of NMS associated with clozapine has been reported to be lower than first generation antipsychotics. However, recent studies suggest that NMS associated with clozapine is likely to be an atypical presentation characterized by less rigidity.[11] This makes it imperative for clinicians to monitor patients closely for any subtle signs or symptoms of NMS, such as tachycardia.[12]

The risks of rapid titration cannot be understated. There is the potential for life threatening side effects such as hypotension, seizures, agranulocytosis, myocarditis, and neuroleptic malignant syndrome. There is also the theoretical potential for rapid titration to result in prescribing a higher dose than necessary. Another factor that must be considered is the impact on side effects on treatment adherence, which raises the question of if a rapid titration may be associated with greater risks of side effects and subsequent discontinuation of treatment. Given that clozapine is often viewed as the last hope for patients, it is crucial that we examine factors that impact long term adherence.

There remains a need for large, randomized, double blinded clinical trials to systematically assess the safety of rapid clozapine titration. This may allow for the identification of risk factors associated serious adverse reactions of rapid titration, such as age, poor oral intake, and concomitant usage of other medications. Rapid clozapine titration has implications for decreasing health care costs associated with prolonged hospitalizations, and decreasing the emotional suffering associated with uncontrolled symptoms of psychosis.[8-10] Clozapine is considered the most effective antipsychotic available thus efforts should focus on developing strategies that would allow for safest and most efficient use of clozapine to encourage its utilization for treatment resistance schizophrenia.

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