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Do Two Rights Make a Wrong? A Case Report on Reversible Neurotoxicity Induced by Coadministration of Clozapine and Lithium

David D. Masolak, M.D., Susanna Ciccolari Micaldi, M.D., M.A.
University of Kansas School of Medicine-Wichita, Wichita, KS
Department of Psychiatry and Behavioral Sciences

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INTRODUCTION

The combination of clozapine and lithium can be utilized in the treatment of refractory schizophrenia, schizoaffective disorder, and bipolar disorder with rapid cycling. Lithium induces leukocytosis which improves bone marrow suppression caused by clozapine but it has a very narrow therapeutic window.[1] When lithium blood concentration is kept within therapeutic levels it is regarded, by and large, as a safe medication.[2] Lithium's therapeutic range lies between 0.30 and 1.30 mEq/liter with 1.50 mEq/liter representing the lower limit for toxicity.[3] At levels above 2.0 mEq/liter, patients experience symptoms of lithium toxicity including nausea, vomiting, diarrhea, tremor, hyperreflexia, ataxia, fasciculations, spasticity, rigidity, extrapyramidal symptoms, seizure, stupor, and coma.[4]

The effectiveness of lithium has been confirmed and it is regarded as a cornerstone of long-term treatment for bipolar disorder and schizoaffective disorder.[5] The Canadian psychiatrist, Paul Grof, introduced the term "excellent lithium responders" for patients who responded to lithium monotherapy with no further recurrences of their illness.[6] However, the percentage of patients in remission from their affective illness on lithium monotherapy was only about one-third.[7] Therefore, in lithium "non-responders", it is necessary to consider different therapeutic agents. Other mood stabilizers, such as, valproic acid or carbamazepine may be used as alternative or adjunctive drugs with good results.[8] Antipsychotics, alone or in combination with lithium, are considered appropriate first line options in acute mania, independent of the presence of psychotic features.[9] Most recently, clozapine in combination with lithium is used for refractory schizophrenia,[10] schizoaffective disorder,[11] and bipolar disorder.[12]

There is a paucity of literature on the combination of these agents and the potential side effects or interactions that can occur. Blake et al.[13] reported four cases in which patients experienced reversible neurologic symptoms while taking clozapine and lithium, despite the blood concentrations of both medications remaining within the therapeutic range. They concluded that achieving lithium levels no greater than 0.5 mEq/liter might yield therapeutic results while minimizing side effects. Another case report by Lee et al.[14] discussed a case of a patient with bipolar disorder treated with clozapine and lithium who developed reversible toxic neurologic symptoms even though the lithium concentration was below 0.5 mEq/L. These reports described adult patients and there are no known published findings about the adolescent population.

In this report, a challenging case of an adolescent is presented who, while taking a combination of lithium and clozapine, appeared to develop reversible toxic neurologic symptoms with a lithium concentration below 1.30 mEq/liter.

CASE REPORT

A 16-year-old female with a past psychiatric history of major depressive disorder with psychotic features and cannabis use disorder was hospitalized at our institution for increasing aggression, disorganization, and hallucinations including command auditory hallucinations to kill her family. The patient had two previous psychiatric admissions, and, at her last hospitalization discharge, two years prior, she was prescribed olanzapine and sertraline.

This was an arduous case because of the patient's lack of cooperation and her family's inability to provide pertinent information including her developmental history. It was concluded that the patient had not seen a psychiatrist for over a year, had stopped going to school due to overwhelming anxiety, and had not left the home for over six months at the time of her third hospitalization. Moreover, during that six-month period, she had not talked to her family and had mostly isolated to her room until the week leading up to her third admission. At that time, the patient was brought to the emergency department because she became violent against her family as they tried to interact with her. At the time of her admission to the hospital, she was responding to internal stimuli and displaying disorganized behavior, such as, laughing inappropriately and displaying abnormal oral-facial movements.

On admission, the patient, who was obese, was started on aripiprazole 2 mg daily for symptoms of psychosis due to concern for further weight gain and metabolic adverse effects from olanzapine to which she had a positive response in the past. The following day, escitalopram 5 mg was started for symptoms of depression and social anxiety. During the first few days of her hospitalization, the patient displayed self-care failure by refusing to shower or brush her teeth, was irritable, and mostly isolated to her room, refusing to attend group therapy.

Aripiprazole was titrated upward and reached 10 mg on hospital day seven with good tolerability. On hospital day 11, escitalopram was increased to 10 mg to target the patient's depressive and anxiety symptoms. Two days later, on hospital day 13, the patient's speech became more pressured and rapid. She began to sleep less with nursing reporting only four hours of sleep at night. The patient also was seen pacing the halls and presented with psychomotor agitation. Her mood became extremely irritable, and she expressed grandiose delusions, such as, graduating from college, owning the hospital where she was admitted, being rich and being married to multiple husbands. This change in mental status was conceptualized as a possible SSRI-induced activation or precipitation of a manic episode, hence, the patient's escitalopram was decreased to 5 mg daily. Aripiprazole did not appear to improve the patient's psychotic symptoms and, over concern for akathisia, on hospital day 14, this medication was stopped by cross tapering it with olanzapine, to which the patient positively responded to in the past.

Based on important information finally obtained by the patient's prior outpatient provider, a few important details provided by the family, and the patient's response to escitalopram, it was concluded that the patient suffered from schizoaffective disorder, bipolar type, two weeks

into her hospital stay. Escitalopram was discontinued and lithium 300 mg twice a day was initiated. Due to the persistence of manic symptoms, lithium initially was increased to 300 mg in the morning and 600 mg at bedtime on hospital day 21, and on hospital day 26 to 600 mg twice a day after her lithium level was found to be 0.65 mEq/L and she was still symptomatic. The patient's olanzapine was titrated slowly up to 12.5 mg at bedtime. However, the patient could not tolerate this increased dose due to excessive sedation hence olanzapine was tapered down to 10 mg at bedtime. On hospital day 32, the patient's lithium level was 0.70 mEq/L, and the dose was increased to 600 mg in the morning and 900 mg at bedtime. On this dose, the patient's lithium level was 0.83 mEq/L when re-checked seven days later.

During the following days, the patient continued to be disorganized, illogical, and endorsed paranoid and grandiose delusions. Due to the patient not tolerating an increase in olanzapine, it was decided to try a different antipsychotic. After carefully sifting through the available information, it became clear that the patient had failed two adequate trials of antipsychotic medications and was treatment resistant. The hospital pharmacist agreed that it would be worthwhile to start the patient on clozapine. On hospital day 39, the patient was started on clozapine 12.5 mg at bedtime. Clozapine was increased gradually to 50 mg in the morning and 100 mg at bedtime by hospital day 55. During this time, the patient became overly sedated. She began sleeping more and started to refuse to leave her room. Four days later, on hospital day 59, the patient was reported to have a coarse hand tremor.

On neurologic and physical exam, the patient had stable vital signs, but displayed lethargy, hyperhidrosis, and a slightly unsteady gait with possible ataxia as she was seen using the wall for assistance. The patient was not cooperative with testing for deep tendon reflexes, myoclonus, or more formal ataxia testing. She also endorsed nausea but was unsure whether she had diarrhea. The patient's lithium level came back at 1.23 mEq/L and lithium was decreased to 600 mg twice a day with a further decrease the next day to 300 mg twice a day. The patient's neurological symptoms subsided except for continued lethargy. Lithium was decreased further and discontinued completely on hospital day 64. Clozaril was titrated gradually up until the patient was taking 50 mg in the morning and 150 mg at bedtime on hospital day 66. The patient's neurotoxic symptoms resolved after lithium was discontinued.

It was initially difficult to differentiate the patient's increased sedation due to lithium toxicity from the antihistaminergic effect of clozapine. By the time of the patient's discharge from the unit on hospital day 70, her sedation had improved but she was mildly disorganized even though she appeared to have improved as compared with her presentation at admission. At the time of discharge, the patient's delusions and hallucinations had resolved and she was no longer aggressive and a danger to self or others.

Since discharge from the hospital, the patient was followed in the outpatient psychiatric clinic. She continued to be compliant with clozapine 50 mg every morning and 150 mg at bedtime with vast improvement in psychiatric symptoms and did not experience any neurologic sequela. At clinic encounters, the patient became more cooperative, pleasant, organized, and talkative with a reactive affect. She isolated much less at home and spent time with her family. Her anxiety improved to the point that she left the home to go to social events and liked to go shopping. She has not had any aggressive episodes or experienced hallucinations or delusions. The family reported that the patient could take care of herself and her pets. The patient had been showering regularly and cooking for herself. Her mother was pleased to see her help with chores around the home.

DISCUSSION

This patient case suggested that typical clinical practice needs to be adjusted in certain circumstances. Normally, it is sensible to achieve a lithium concentration of 0.30 to 1.30 mEq/L and concentrations above 1.50 mEq/L begin to raise concern for lithium toxicity. For our patient, her neurotoxic symptoms developed when clozapine was added to her lithium regimen with a level of 0.83 mEq/L. The patient was tolerating lithium well prior to this addition and no change in dose was made to lithium. The temporal correlation along with the pathognomonic signs and symptoms were highly suggestive of lithium toxicity.

Blake et al.[13] described four patients treated with the combination of clozapine and lithium who developed reversible neurologic symptoms. For those patients, the clozapine dose was 900 mg daily and the lithium dose was between 900 and 1,200 mg daily. The lithium blood concentrations ranged from 0.7 to 0.8 mEq/L.

Our patient was on a lower dose of clozapine totaling 150 mg daily but on a higher dose of lithium (1,500 mg daily). Prior to the initiation of clozapine, on this lithium dose, our patient had a lithium level of 0.83 mEq/L. After the addition of clozapine, the patient's lithium level increased to 1.23 mEq/L, with no change in lithium dose. In the literature, there was no evidence of a drug-drug interaction between lithium and clozapine. Lithium is an intracellular ion that is not metabolized by the liver but is excreted purely by the kidneys while clozapine depends on the cytochrome P450 1A2 for its metabolism.[15]

The mechanism for the increased risk of neurotoxicity when lithium is combined with clozapine is unknown. The combined serotonergic effect of clozapine and lithium has been proposed as a possible culprit.[16] Therefore, one important recommendation for providers is to use caution when prescribing this combination. Decreased dosages of both medications and stringent monitoring of side-effects seem to be crucial. Also, it is important to monitor continually the mental status of patients taking a combination of lithium and clozapine. If there is any concern for toxicity, more frequent lithium concentration levels should be obtained. Blake et al.[13] suggested that when combined with clozapine, the lithium concentration should be kept at no more than 0.5 mEq/L.

The final lesson from our patient was related to clozapine delayed treatment response. The delay to onset hypothesis for antipsychotics has been refuted in the past.[17] In fact, treatment response to antipsychotics began in the first week and accumulated over time, with greater improvement in the first two weeks compared to the subsequent two weeks.

Conversely, clozapine efficacy in the treatment-resistant population

has long observation periods lasting up to 20 months.[18] It took several weeks for our patient's symptoms to ameliorate appreciably, and they continued to improve in the outpatient setting on the same clozapine regimen. This result highlighted the importance of using patience when assessing the efficacy of clozapine which will take many weeks to be fully paramount.

REFERENCES

[1] Small JG, Klapper MH, Malloy FW, Steadman TM. Tolerability and efficacy of clozapine combined with lithium in schizophrenia and schizoaffective disorder. J Clin Psychopharmacol 2003; 23(3):223-228. PMID: 12826983.
[2] Arya DK. Lithium-induced neurotoxicity at serum lithium levels within the therapeutic range. Aust N Z J Psychiatry 1996; 30(6):871-873. PMID: 9034481.
[3] Amdisen A. Serum concentration and clinical supervision in monitoring of lithium treatment. Ther Drug Monit 1980; 2(1):73-83. PMID: 6762704.
[4] McKnight RF, Adida M, Budge K, Stockton S, Goodwin GM, Geddes JR. Lithium toxicity profile: A systematic review and meta-analysis. Lancet 2012; 379(9817):721-728. PMID: 22265699.
[5] Geddes JR. Burgess S, Kawton K, Jamison K, Goodwin GM. Long-term lithium therapy for bipolar disorder: Systematic review and meta-analysis of randomized controlled trials. Am J Psychiatry 2004;161(2):217-222. PMID: 14754766.
[6] Grof P. Excellent lithium responders: People whose lives have been changed by lithium prophylaxis. In: NJ Birch, VS Gallicchio, RW Becker (Eds). Lithium: 50 Years of Psychopharmacology, New Perspectives in Biomedical and Clinical Research. Cheshire, CT: Weidner Publishing Group, 1999, pp 36-51. ISBN: 0964107368.
[7] Rybakowski JK, Chlopocka-Wozniak M, Suwalska A. The prophylactic effect of long-term lithium administration in bipolar patients entering lithium treatment in the 1970s and 1980s. Bipolar Disord 2001 3(2):63-67. PMID: 11333064.
[8] Calabrese JR, Woyshville MJ. A medication algorithm for treatment of bipolar rapid cycling? J Clin Psychiatry 1995; 56(Suppl 3):11-8. PMID: 7883737.
[9] Yatham LN, Kennedy SH, Parikh SV, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) 2018 guidelines for the management of patients with bipolar disorder. Bipolar Disord 2018; 20(2):97-170. PMID: 29536616.
[10] Meltzer HY. Treatment of the neuroleptic-nonresponsive schizophrenic patient. Schizophr Bull 1992; 18(3):515-542. PMID: 1357741.
[11] Zarate CA Jr, Tohen M, Baldessarini RJ. Clozapine in severe mood disorders. J Clin Psychiatry 1995; 56(9):411-417. PMID: 7665540.
[12] Suppes T, Phillips KA, Judd CR. Clozapine treatment of nonpsychotic rapid cycling bipolar disorder: A report of three cases. Biol Psychiatry 1994; 36(5):338-340. PMID: 7993960.
[13] Blake LM, Marks RC, Luchins DJ. Reversible neurologic symptoms with clozapine and lithium. J Clin Psychopharmacol 1992; 12(4):297-299. PMID: 1527237.
[14] Lee SH, Yang YY. Reversible neurotoxicity induced by a combination of clozapine and lithium: A case report. Zhonghua Yi Xue Za Zhi (Taipei) 1999; 62(3):184-187. PMID: 10222608.
[15] de Leon J, Ruan CJ, Schoretsanitis G, De Las Cuevas C. A rational use of clozapine based on adverse drug reactions, pharmacokinetics, and clinical pharmacopsychology. Psychother Psychosom 2020; 89(4):200-214. PMID: 32289791.
[16] Lemus CZ, Lieberman JA, Johns CA. Myoclonus during treatment with clozapine and lithium: The role of serotonin. Hillside J Clin Psychiatry 1989; 11(2):127-130. PMID: 2488054.
[17] Agid O, Kapur S, Arenovich T, Zipursky RB. Delayed-onset hypothesis of antipsychotic action: A hypothesis tested and rejected. Arch Gen Psychiatry 2003; 60(12):1228-1235. PMID: 14662555.
[18] Raguraman J, Vijay Sagar KJ, Chandrasekaran R. Effectiveness of clozapine in treatment-resistant schizophrenia. Indian J Psychiatry 2005; 47(2):102-105. PMID: 20711291.

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