Relationship Between Clozapine Levels and Acute Inflammatory Stress

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ABSTRACT

Stress-induced changes in pharmacokinetics can significantly alter the plasma levels of some drugs such as clozapine. This report describes the case of a middle-aged man with schizoaffective disorder, bipolar type who showed sustained elevation in clozapine levels 3 days after discontinuation. Before the clozapine levels were drawn, he had developed acute bacterial pneumonia and signs of acute bacterial meningitis followed by neuroleptic malignant syndrome after he received multiple doses of intravenous haloperidol for worsening psychosis and aggressive behavior. Existing literature on this topic is also reviewed to investigate potential reasons for sustained clozapine levels during acute inflammatory stress and neuroleptic malignant syndrome.

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Clozapine is still considered a gold standard in the management of treatment-refractory schizophrenia. However, despite its proven efficacy, clozapine has not been accepted as a first-line treatment for schizophrenia due to multiple clinically serious adverse effects, including agranulocytosis and lowering of seizure threshold. Although these adverse effects are rare, they are well known to prescribers and closely monitored due to their clinical seriousness. But, there is less awareness of the risks associated with different types of drug interactions, including drug-disease interactions, in which an acute medical stress can alter the plasma level of drugs such as clozapine to further complicate psychiatric and physical health in medically vulnerable patients. Here, we review existing literature and describe the case of a middle-aged man with acute bacterial pneumonia/meningitis and haloperidol-induced neuroleptic malignant syndrome who developed sustained toxic levels of clozapine 3 days after discontinuation.

CASE REPORT

The patient was a 51-year-old white man with treatment-refractory schizoaffective disorder, bipolar type along with tobacco use disorder, obesity, hyperlipidemia, recurrent pneumonia, and chronic cough. He was stable enough on clozapine 450 mg/day augmented with lamotrigine 25 mg/day to live independently in an apartment. However, before admission to the hospital, he had presented to urgent care with flu-like symptoms along with unyielding auditory hallucinations. He was given acetaminophen 1,000 mg and oseltamivir 75 mg prior to being sent home. However, he continued to experience severe headache and auditory hallucinations and was taken to the emergency department.

At the hospital, the patient was found to have a fever of 102.6°F, tachycardia with a pulse of 117 bpm, and hypertension with a blood pressure of 146/77 mm Hg. He was only communicative with nonverbal cues and nodded in affirmation when asked about auditory hallucinations. He was observed repeatedly mimicking a smoking action with his pulse oximeter and on physical examination was found to have muscle rigidity of the neck and upper and lower extremities but with no change in muscle tone. Laboratory workup revealed mild leukocytosis (13.67 mm^3) and a mildly toxic lactate level of 3.4 mmol/L; however, metabolic profile (except blood sugar level of 206 mg/dL), thyroid-stimulating hormone, T_4, creatine kinase, ammonia, procalcitonin, urinalysis, and alcohol and urine drug screen findings were unremarkable. Blood cultures were positive for streptococcus pneumonia, and a chest x-ray revealed bilateral pulmonary infiltrates. The patient's fever remained around 102.5°F during this time, probably due to repeated use of acetaminophen.

Medical staff attempted to perform a spinal tap, as the patient had neck rigidity, but could not do so successfully due to writhing movements. He was admitted to the medical unit for the treatment of

Clinical Points

- There are clinically meaningful interactions between clozapine levels and acute inflammatory stress.
- Clozapine plasma levels may significantly increase during acute bacterial infections.
- Monitoring of clozapine levels may help in the detection of clozapine toxicity and prevention of complications in a medically vulnerable patient population.

severe sepsis, most likely secondary to bacterial pneumonia and potentially meningitis, and began treatment with broad-spectrum antibiotics. The patient's fever, leukocytosis, and writhing movements decreased to allow for spinal tap, which revealed bacterial meningitis, most likely from the same bacteria that was found earlier in his blood cultures. However, his procalcitonin and lactate levels increased dramatically accompanied by encephalopathy, as reflected by agitation and verbal and physical aggression toward staff. These symptoms were treated with 5 consecutive doses of intravenous haloperidol 5 mg within 24 hours, which was followed by a relapse in fever with altered mental state, tachycardia, tachypnea, diaphoresis, increased blood pressure, tremors, confusion, and muscle rigidity. Neuroleptic malignant syndrome was diagnosed after laboratory values revealed a creatine kinase level of 3,200 U/L along with some elevation in liver enzymes (aspartate aminotransferase = 196 U/L, alanine aminotransferase = 126 U/L). However, instead of leukocytosis, a decline in leukocyte (9.92 to 6.90 mm^3) and neutrophil (11.91 to 5.62 mm^3) count was observed, possibly due to sepsis.[1]

The patient was admitted to the intensive care unit to manage neuroleptic malignant syndrome with supportive care measures including lorazepam, cooling blankets, and close observation of vital signs. These measures failed to decrease his fever or leukocyte count, thus he was started on dantrolene. Treatment with dantrolene resulted in rapid improvement in fever, leukocytosis, and mental status as well as normalization of vital signs, and he was transferred out of the intensive care unit. Surprisingly, a clozapine level ordered 60 hours after the last bedtime dose of 250 mg revealed a clozapine and norclozapine level of 1,242 ng/mL. Of note, the patient had stopped smoking (ie, 1 pack/day) after his previous visit to the emergency department before this hospitalization. Interestingly, a similar dose of clozapine (ie, 450 mg/d) approximately 10 months ago produced a total clozapine and norclozapine level of 533 ng/mL (Table 1).

Clozapine Plasma Levels

The only baseline clozapine levels were 333 ng/mL for clozapine and 200 ng/mL for norclozapine on a daily dose of 450 mg/d. The second levels, drawn about 8 months later, were 889 ng/mL for clozapine and 353 ng/mL for norclozapine after 60 hours of a bedtime dose of clozapine 250 mg. The second level was assessed 1 to 2 days after the patient was diagnosed with bacterial pneumonia.

Clozapine/Norclozapine Ratio

The clozapine/norclozapine ratio is calculated by dividing clozapine with norclozapine plasma levels. This ratio was 1.67 at baseline. However, this ratio significantly increased to 2.52 at the second clozapine level assessment.

DISCUSSION

Several case reports and case series[2–11] have documented changes in clozapine levels in response to acute inflammatory stress. Each of these cases, including the present case, has enhanced our understanding of various clinical aspects of this highly complex interaction between clozapine levels and inflammatory stress (drug-disease interaction). One such aspect that is unique to our case is that the unusual increase in clozapine levels could have been easily missed due to medical comorbidities and their treatment if clozapine levels were not requested 3 days after its discontinuation. It was the sustained clozapine level that initiated further investigation into this case (Table 1).

To begin with, smoking is highly relevant to this case, as hydrocarbons in cigarette smoke are known to lower clozapine levels through induction of cytochrome P450 (CYP) enzyme 1A2, which provides the main metabolic pathway for clozapine.[12,13] Hence, clozapine levels rebound after smoking is discontinued,[2] as happened in our patient. However, this explanation is unlikely since our patient was within 60 hours of smoking discontinuation and increased clozapine levels are not observed earlier than 14 days after smoking discontinuation.[14] Clozapine overdose could also explain unusually high clozapine levels before the patient presented to urgent care. However, the patient's medical records revealed a long history of medication adherence. Nevertheless, an accidental clozapine overdose during an altered state of mind cannot be completely ruled out. Concomitant use of metoprolol and repeated doses of intravenous haloperidol are also unlikely to solely explain high clozapine levels, as CYP2D6, which metabolizes both metoprolol and haloperidol, does not provide the primary metabolic pathway for clozapine's metabolism to norclozapine.[12] Other concomitant medications (ie, analgesics and antibiotics) are also unlikely to alter clozapine levels significantly. In addition, an organ dysfunction secondary to bacterial sepsis and neuroleptic malignant syndrome could contribute toward an increase in clozapine levels, but a normal metabolic profile makes it unlikely.

A literature review[15] revealed 2 plausible mechanisms underlying an unusual increase in clozapine levels in patients during inflammatory stress. The first mechanism is stress-induced increase in the clozapine-binding plasma protein α-1-acid glycoprotein.[16] One case report[8] found a 50% increase in α-1-acid glycoprotein during acute illness. This finding is significant because clozapine is about 95% protein bound and its metabolites N-desmethylclozapine and clozapine N-oxide are also 90% and 75% protein bound, respectively.[4] Thus, an increase in α-1-acid glycoprotein can increase the binding capacity of both clozapine and

Table 1. Time Relationship Between Clozapine Doses, Clozapine and Norclozapine Levels and Ratio, Concomitant Medications, Clinical Condition, and Smoking Status

Date[a]	Clozapine Dose (mg/d)	Clozapine Levels (ng/mL)	Norclozapine Levels (ng/mL)	Clozapine/ Norclozapine Ratio	Concomitant Medications	Clinical Condition	Location	Smoking Status
6/27/18	450	333	200 ng/mL	1.67	Scheduled: atorvastatin 20 mg, vitamin D_3 2,000 IU, lurasidone 60 mg, olanzapine 10 mg PRN only once		Inpatient psychiatry	No smoking, on nicotine patch; patient started smoking as an outpatient
4/14/19	450	NA	NA				Outpatient	Smoking 1 pack/d
4/15/19	250	NA	NA		Received last clozapine dose of 250 mg by mouth at 8:30 pm Scheduled: acetaminophen 2,000 mg, piperacillin, tazobactam 4.5 g	Headache, AMS, blood culture positive for pneumococcus, temperature: 102.6°F, heart rate: 117 bpm, blood pressure: 146/77 mm Hg	Outpatient Admitted to medical floor at 8:04 pm	Smoking 1 pack/d
4/16/19	Discontinued	NA	NA		PRN: haloperidol 5 mg IV at 6:51 pm, haloperidol 5 mg IV at 9:32 pm Scheduled: vancomycin 2,000 mg, azithromycin 500 mg, ceftriaxone 1,000 mg, metoprolol 25 mg, nicotine patch 14 mg, acetaminophen 650 mg, lovenox 40 mg	Continued AMS, worsening HTN, persistent fever; diagnosed with bacterial pneumonia	Inpatient medical floor	No smoking
4/17/19	Discontinued	NA	NA		PRN: haloperidol 5 mg IV at 3:53 am, haloperidol 5 mg IV at 8:47 am, haloperidol 5 mg IV at 2:23 pm Scheduled: vancomycin 2,000 mg, azithromycin 500 mg, ceftriaxone 1,000 mg, metoprolol 25 mg, nicotine patch 14 mg, acetaminophen 650 mg, enoxaparin 40 mg	Patient begins writhing, severe rigidity CK > 3,200 U/l at 6:39 am		
4/18/19	Discontinued	889	353	2.52	Scheduled: acyclovir 1,460 mg, azithromycin 250 mg, ceftriaxone 4 g, enoxaparin 40 mg, lorazepam 1 mg, vancomycin 1,750 mg, tylenol 325 mg, dilaudid 0.5 mg, nicotine patch 14 mg, dantrolene 245 mg	Continued AMS, HTN, persistent fever, writhing, persistent rigidity; diagnosed with NMS; CSF cell count indicated pneumococcal meningitis	Inpatient medical floor	No smoking
4/23/19	Discontinued	< 100	< 100	NA	Scheduled: same as above except dantrolene was discontinued in 2 days	Cleared sensorium, mental status intact, normal vital signs, no rigidity	Inpatient medical floor	No smoking

[a]Dates have been changed to protect patient anonymity.
Abbreviations: AMS = altered mental status, CK = creatinine kinase, CSF = cerebrospinal fluid, HTN = hypertension, IV = intravenous, NA = not available, NMS = neuroleptic malignant syndrome, PRN = as needed.

norclozapine. The outcome is an increase in the protein-bound clozapine and norclozapine levels without affecting the plasma levels for unbound and biologically active clozapine.[11] Since protein-bound clozapine is biologically inactive, any increase in protein-bound clozapine is unlikely to result in adverse effects.

The second underlying mechanism is inhibition of CYP1A2, which is responsible for 70% of clozapine's metabolism[7] by stress-induced increase in proinflammatory markers such as interleukin-6 (IL-6),[4] IL-1β, tumor necrosis factor-α, and α or γ interferons.[2] Since CYP1A2 mediates clozapine's biotransformation to norclozapine, an increase in the clozapine/norclozapine ratio from 1.67 (based on levels drawn 10 months previously) to 2.52 in our patient suggests inhibited activity of CYP1A2, which is consistent with similar increases in the clozapine/norclozapine ratio observed in several other reports.[5,8,9] In 1 review,[7] clozapine metabolism seemed to decrease by a factor of 2, specifically during a respiratory infection. In another study,[17] the total change in clozapine levels during inflammation was measured using the concentration per dose of clozapine levels in the setting of elevated levels of C-reactive protein (CRP), which is the most accurate marker available to monitor inflammation. The results revealed the highest increase (ie, 48%) in clozapine levels compared to risperidone (ie, 24.2%) and quetiapine (11.9%) levels.[17] This finding[17] suggests that CRP can be employed as a useful marker for inflammation and, in turn, toxic clozapine levels.

Unlike increase in protein-bound inactive clozapine, increase in biologically active clozapine due to inhibition of CYP1A2 by proinflammatory markers can be associated with adverse effects such as myoclonus, hypotension, sialorrhea, obtundation,[8] aphasia, akinesia, incoherence of speech, and gait disturbance.[9] Despite being masked by acute medical comorbidities, some of these adverse effects could have contributed to the bacterial infection in our patient. It is at least theoretically possible that the relatively mild leukocytosis observed in this

patient, despite acute bacterial infection and neuroleptic malignant syndrome, could be due to neutropenic effects of clozapine. Another frequently observed factor in this patient population, which increases susceptibility to respiratory infections, is smoking and the negative effects it has on cilia.[4] Clozapine toxicity can also be increased by its biotransformation to nitrenium ions, which can induce proinflammatory response, thus further contributing to the acute inflammatory stress and inhibitory effects of proinflammatory markers on clozapine metabolism.[18] Furthermore, during acute inflammation, clozapine molecules can act as haptens, resulting in hypersensitivity reactions.[4] For these reasons, it can be extremely difficult to differentiate adverse effects of clozapine toxicity from the signs and symptoms of acute medical comorbidities as observed in this report.

CONCLUSION

This case exemplifies the complex interplay between clozapine pharmacokinetics and acute inflammatory stress secondary to acute bacterial infections. Although the adverse effects from toxic clozapine levels in our patient are difficult to separate from those caused by acute medical comorbidities, monitoring of clozapine levels during acute bacterial infections may help detect clozapine toxicity and prevent further complications in medically vulnerable patients.

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