

# Toxic clozapine level as first indication of severe, acute infection

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**How to cite:** Davis EAK, Hightower T, Cinnamon KA. Toxic clozapine level as first indication of severe, acute infection. *Ment Health Clin* [Internet]. 2022;12(1):45-8. DOI: 10.9740/mhc.2022.01.045.

**Submitted for Publication:** May 26, 2021; **Accepted for Publication:** December 1, 2021

## Abstract

**Background:** Clozapine levels can be influenced by many factors, including pharmacogenomic variability, pharmacokinetic drug interactions, and infection/inflammation. The concentration-to-dose ratio (C/D), a measure of a medication's rate of metabolism and clearance, may increase during an acute infection due to decreased medication metabolism and clearance.

**Case Report:** A 56-year-old White man was restarted on clozapine and titrated up to 350 mg/d with therapeutic steady-state levels (C/D 1.11) on hospital day (HD) 69. At this time, he was also being treated for COPD exacerbation. For the next month, he continued to complain of cough, but vital signs and chest x-ray remained normal. Labs were unremarkable except for occasional leukocytosis that would resolve on repeat evaluation. A routine clozapine level drawn on HD 104, resulted on day 108 and showed clozapine toxicity with C/D 4.05, although the patient was asymptomatic. After receipt of labs on day 109, showing elevated WBC count, he was immediately sent to the emergency room where he was admitted for treatment of pneumonia. On return to the state hospital, the patient was continued on 100 mg clozapine and titrated to 200 mg/d based on low drug levels. He continued to do well on 200 mg/d clozapine with C/D averaging 1.13 (range, 0.75-1.52).

**Discussion:** Acute infection and illness can lead to significantly increased clozapine levels and toxicity, even if symptoms of toxicity are minimal or absent. This appears to be the first report of a toxic level being the first indication of severe medical illness.

**Keywords:** clozapine, toxicity, infection, therapeutic drug monitoring, CYP1A2

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**Disclosures:** The authors have nothing to disclose.

## Background

Clozapine is the most efficacious antipsychotic but is reserved for treatment-resistant schizophrenia owing to

potentially serious side effects.<sup>1</sup> Although there is significant intra- and interindividual variability of plasma levels, the threshold where risks outweigh the benefits is often considered to be 1000 mcg/L or higher.<sup>2,3</sup> Clozapine is metabolized primarily by cytochrome P450 isoenzyme 1A2 (CYP1A2) to its major metabolite, N-desmethylozapine (norclozapine). Clozapine and norclozapine levels can be influenced by many factors including genotype, pharmacokinetic drug-drug interactions, smoking, excessive caffeine, and infection/inflammation.<sup>2-7</sup> Acute infection and inflammation can reduce expression of CYP1A2 by up to 90% due to an increase in inflammatory cytokines such as interleukin-6, interferon, and tumor

necrosis factor- $\alpha$ . This reduction in CYP1A2 can result in significantly elevated clozapine levels due to decreased metabolism.<sup>8-10</sup>

At steady state, the rate of metabolism and clearance can be measured by the medication's concentration-to-dose ratio (C/D).<sup>11</sup> For clozapine, the C/D ratio is typically obtained by dividing the clozapine concentration by the clozapine dose with normal values between 0.6 and 1.2.<sup>11-13</sup> Higher C/D ratios may be seen in females, non-smokers, those of Asian descent, CYP1A2-poor metabolizers, those with concomitant CYP1A2 inhibitors, obese individuals, and those with acute inflammation.<sup>14</sup> Lower C/D ratios may indicate a lack of adherence or higher medication clearance owing to male sex, smoking, non-Asian ethnicity, and those with concomitant CYP1A2 inducers. Another measure commonly used is the clozapine-to-norclozapine (C/N) ratio, with a ratio of  $>2$  suggesting saturated metabolism.<sup>15,16</sup> This case describes a patient with a significant increase in clozapine level identified prior to the diagnosis of pneumonia and allows for comparison of levels before, during, and after infection. This appears to be the first case report of a toxic clozapine level prompting further evaluation and eventual diagnosis of severe, acute infection.

## Case Report

A 56-year-old White man with schizoaffective disorder, bipolar type was admitted to a locked nonsmoking state psychiatric hospital on emergency petition. Several antipsychotics were trialed with minimal response. Since he was stabilized and discharged on clozapine 400 mg/d during a previous admission (clozapine and norclozapine levels 488 and 152 mcg/L, respectively; C/D 1.22), the decision was made to restart this medication, which was started on hospital day (HD) 51. The dose was titrated up to 350 mg/d (150 mg in the morning and 200 mg at night) by HD 63, and a steady-state level 12 hours post-dose on HD 69 showed clozapine and norclozapine levels of 390 mcg/L and 137 mcg/L, respectively (C/D 1.11). Other psychiatric medications at this time included bupropion XL 150 mg, divalproex 2250 mg/d, lorazepam 1 mg twice a day, olanzapine 15 mg twice a day, and risperidone 3 mg twice a day. It should also be noted that, at the time of this level, the patient was on day 4 of a 5-day course of oral antibiotics and corticosteroids for treatment of a COPD exacerbation. A chest x-ray revealed no pneumonia or effusion, he remained afebrile, and labs were unremarkable.

Despite finishing a course of antibiotics and oral corticosteroids, the patient continued to complain of a cough on HD 84 resulting in as-needed use of guaifenesin and albuterol inhaler. He remained afebrile with oxygen

saturation in the mid-90s. Respirations were even and unlabored, and no distress was noted. Another chest x-ray was completed that was unremarkable except for mild bilateral linear atelectasis. The cough persisted off and on with continued occasional use of guaifenesin and albuterol for another 3 weeks. Labs during this time were unremarkable with occasional leukocytosis that would resolve on repeat evaluation. A repeat clozapine level was drawn on HD 104, but because it is a "send-out" lab, the results were not received for 4 days. At this point, the patient's other psychiatric medications included only divalproex 2250 mg/d and lorazepam 0.5 mg twice a day.

On HD 108, the results were received that showed clozapine and norclozapine levels of 1419 mcg/L and 463 mcg/L, respectively (C/D 4.05). The on-call psychiatrist was notified and considered sending the patient to the emergency room but ultimately decided against it since the patient was not exhibiting any signs of toxicity. Instead, the psychiatrist ordered to hold clozapine with a follow-up level the next day to rule out lab error. The following day, HD 109, the attending psychiatrist conferred with the clinical pharmacist and could not determine a cause for the increased level given that it was drawn 12 hours after the last dose, the dose had not changed, and there were no interacting medications. The possibility of an infection was discussed because of the patient's continued cough, despite no objective evidence, and STAT labs were added to the repeat clozapine level. At this time, he was given a one-time dose of clozapine 50 mg.

Later that day, on HD 109, results were received indicating WBC count 21.6 thousand/ $\mu$ L and ANC, 17.8 thousand/ $\mu$ L. Because of these results, the decision was made to send the patient to the emergency room, where he was diagnosed with pneumonia and admitted to the acute care hospital for 5 days. The clinical pharmacist was again consulted and recommended decreasing the total daily dose to 100 mg owing to the presumed effects of acute infection on the clozapine level. Despite this recommendation, the patient continued to receive 250 mg/d while at the acute care hospital. No levels were drawn on this dose. Several days later the results were received for the level obtained on HD 109 (after the medication had been held for 24 hours) and showed clozapine and norclozapine levels of 982 mcg/L and 414 mcg/L, respectively (C/D 3.51). Lorazepam was discontinued while the patient was at the acute care hospital.

On return to the state hospital on HD 114, the clozapine dose was decreased to 100 mg/d, which he was maintained on for several weeks. A new steady-state level on HD 132 showed clozapine and norclozapine of 108 mcg/L and 47 mcg/L, respectively (C/D 1.08), with repeat levels on HD 139 indicating 75 mcg/L and 36 mcg/L,

**TABLE: Laboratory findings and metabolic measurements**

Hospital Day	CLZ Dose (mg/d)	CLZ Level <sup>a</sup> (mcg/L)	NCLZ Level <sup>a</sup> (mcg/L)	C/D Ratio	C/N Ratio
69	350	390	137	1.11	2.85
104 <sup>b</sup>	350	1419	463	4.05	3.06
109 <sup>b</sup>	280 <sup>c</sup>	982	414	3.51	2.37
132	100	108	47	1.08	2.30
139	100	75	36	0.75	2.08
174	200	199	93	1.00	2.14
202	200	197	115	0.99	1.71
237	200	259	132	1.30	1.96
270	200	247	130	1.24	1.90
298	200	219	112	1.10	1.96
328	200	184	97	0.92	1.90
361	200	304	142	1.52	2.14
390	200	287	144	1.44	1.99

C/D = concentration-to-dose; CLZ = clozapine; C/N = clozapine-to-norclozapine; NCLZ = norclozapine.

<sup>a</sup>All levels were drawn 12 hours post-dose.

<sup>b</sup>During infection.

<sup>c</sup>Average dose over preceding 5 days since clozapine was held for 24 hours prior to level (not at steady state).

respectively (C/D 0.75). The decision was made to increase the dose to 200 mg/d on HD 147. The patient continued to do well on 200 mg/d and remained psychiatrically stable until discharge. The C/D ratios ranged from 0.92 to 1.52 with an average of 1.18.

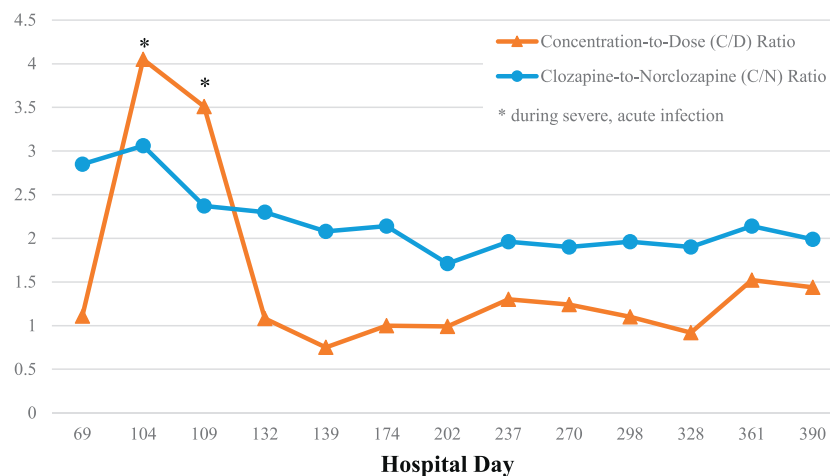
## Discussion

The metabolism of clozapine can be impacted by numerous factors. It is well known that acute infection can lead to increased clozapine levels, namely, through 2 potential mechanisms: reduced expression of CYP1A2 due

to increased inflammatory cytokines, and increase in the acute phase protein,  $\alpha$ -1 acid glycoprotein (AGP).<sup>10,17-19</sup> Clozapine is 95% protein-bound in the plasma and predominantly to this protein.<sup>18</sup> Therefore, an increase in AGP will lead to increased binding capacity of clozapine and an increase in total measured clozapine concentration (protein-bound and free). However, the concentration of unbound drug, which exerts the pharmacologic effects, would not be expected to increase. This may help explain why many cases of elevated clozapine levels during an acute infection do not display symptoms of toxicity, or only minor symptoms in relation to the degree of increase.<sup>3,4,19</sup>

There are several methods of indirectly measuring the metabolic activity of clozapine. Previous reports<sup>3,6,7,11,15</sup> of clozapine toxicity with acute infection demonstrate significant increases in both C/D and C/N ratios, which were not shown in this case. As expected, our patient's C/N was slightly higher during a period of acute infection, indicating decreased metabolism, but the degree of change was relatively small (Table and Figure). On the other hand, our patient's C/D dramatically increased with infection. The variations in C/D, but not C/N, may suggest a mechanism other than CYP1A2 inhibition in the presented case. Unfortunately, no other labs were measured that would allow a better understanding of the mechanism in this case.

What is particularly interesting about the presented case is that a routine elevated clozapine level is what led to further evaluation and eventual diagnosis of acute pneumonia, requiring a 5-day admission to the acute care hospital and treatment with intravenous antibiotics. This appears to be the first published report of a toxic clozapine level being the first indication of severe, acute infection. Last, another unique feature of this case is that



**FIGURE: Changes in clozapine-to-norclozapine and concentration-to-dose ratios before, during, and after a severe, acute infection**

the initial clozapine level was drawn during an exacerbation of the patient's COPD, but there was no indication of decreased clozapine metabolism at that time. Since the effects on clozapine metabolism and drug concentration are mediated by inflammatory cytokines, we would anticipate similar alterations during a COPD exacerbation requiring treatment. It is possible that the 3-day course of oral corticosteroid inhibited inflammatory cytokines that would normally increase clozapine levels. Unfortunately, other labs including C-reactive protein and AGP levels were not measured, preventing any further analysis.

## Conclusion

In conclusion, acute infection and illness can lead to significantly increased clozapine levels and presumed toxicity, but symptoms of toxicity may be minimal or absent. An unexpectedly elevated clozapine level should prompt further evaluation, particularly for acute infection. Further research is needed to elucidate the exact mechanism of the interaction as well as determine which patients and/or types of infections are at greatest risk.

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