The Clozapine-Infection Connection

By Brian Miller, MD, PhD, MPH

Monitoring patients for 5 key changes can help avert drug toxicity. This article examines previous and current studies associated with clozapine and infection.
About Clozapine

• Clozapine is the “gold-standard” antipsychotic for treatment-resistant schizophrenia

• Blood clozapine levels can help guide clinicians to improve response rates and minimize adverse effects from this medication

• Adverse effects of clozapine that may be related to its blood levels include sedation, seizures, arrhythmias, and hypotension¹
Clozapine and Infection

• Case studies have found associations between infections (and their treatment) to elevated clozapine blood levels.

• A previous study found that rechallenge with clozapine was associated with an increased risk of recurrent pneumonia.²

• Severe infections may also inhibit cytochrome P450 enzymes, leading to elevated blood clozapine levels.³
Study Methods

• Clark and colleagues\(^4\) performed a systematic review of studies of elevated blood clozapine levels associated with infection.

• Articles were identified by searching PubMed and Embase with the terms “clozapine, toxicity, infection”.

• The authors defined an elevated clozapine level as either (1) > 1000 mcg/L, or (2) > 600 mcg/L with clinical symptoms of clozapine toxicity.
Study Methods (2)

- Cases with a diagnosis of infection were included.

- Cases of inflammation without a diagnosis of infection, as well as cases with an identifiable non-infectious cause of elevated clozapine levels—such as liver failure and use of fluvoxamine—were excluded.

- Descriptive statistics were calculated for age, sex, diagnosis, clozapine levels, white blood cell (WBC) counts, C-reactive protein (CRP) levels, presence or absence of fever, and type of adverse effects.
Study Results

• The authors identified 23 studies that described 32 cases, and they included an additional 8 cases associated with their own clinical services, for a total of 40 cases.

• The most common diagnosis was treatment-resistant schizophrenia (n = 31).

• Mean age was 49, 58% of cases were male, and the mean duration of clozapine treatment was 4 years.
• Clozapine dosages ranged from 200 to 900 mg/d, and the median baseline clozapine blood level was 550 mcg/L

• The 2 most common types of infections were respiratory (58%) and urinary (33%)

• Fever was absent in 30% of cases, and an elevated WBC count was absent in 25%

• The mean clozapine level during infection was 1811 mcg/L
• The most common adverse effects were sedation (48%) and delirium (20%), and gross neurologic signs were found in over 20% of cases.
• Five cases had no abnormal neurologic signs, despite clozapine levels of > 1000 mcg/L.
• No deaths were recorded.
• In all cases, clozapine dose reduction or discontinuation was associated with resolution of adverse effects over a period of days to weeks.
Discussion

• This systematic review identified 40 cases of elevated blood clozapine levels associated with infection.

• Potential mechanisms of this association include effects of inflammation, antibiotics, and changes in smoking (due to sedation) on cytochrome P450 drug-metabolizing enzymes; and a predisposition to infection with clozapine use.
Discussion (2)

- Fever or elevated WBC counts were absent in about one-quarter of cases, which suggests elevated clozapine levels may inhibit some classic signs of infection.

- By contrast, however, 90% of cases reported elevated levels of the inflammatory marker CRP.

- Limitations of the review include the relatively small sample, retrospective design, and incomplete demographic and clinical data.
- Nevertheless, findings suggest this is a clinically relevant phenomenon.
The bottom line

- Clozapine is associated with infections and may delay the diagnosis of infections in some patients.

Look for 5 key changes:
- Patients who take clozapine and are hospitalized for infection should be monitored for changes in (1) smoking status, (2) mental status, (3) renal function, (4) liver function, and (5) clozapine level.

- Gradual dose reduction of clozapine in these patients may balance the risk of emergent adverse effects of clozapine with worsening of psychotic symptoms.
- Future prospective studies in this area are warranted.


About the author

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