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Cutting in Cloze: Monitoring and Dose Adjustments for Clozapine Toxicity in COVID-19

Clozapine is a second-generation antipsychotic approved for treatment resistant schizophrenia and acute suicidality in schizophrenia and schizoaffective disorder. While clozapine is the most efficacious antipsychotic, it exhibits several dose and titration-dependent adverse events. Orthostatic hypotension, seizures, myocarditis, and cognitive impairment are minimized by slow titration of clozapine with dose increases of 12.5 to 25 mg daily. Accelerated dose titrations or higher doses may result in clozapine toxicity, which may present as delirium, seizures, coma, arrythmias, hypotension, or respiratory failure. Clozapine therapeutic drug monitoring can assist in clozapine dose adjustments while avoiding toxicity. A clozapine level between 300-500 mcg/L and clozapine to norclozapine ratio of 0.5-3 are associated with clinical efficacy. Clozapine levels greater than 600 mcg/L are associated with greater adverse events with limited increased efficacy. Several factors may influence clozapine levels, including drug interactions with smoking, antidepressants as well as inflammation. Elevated c-reactive protein is associated with significant increases in clozapine levels during infection. COVID-19 infection triggers cytokine stimulation, which inhibits CYP1A2 metabolism of clozapine, resulting in clozapine toxicity. Case reports of COVID-19 positive patients also being treated with clozapine demonstrate significantly elevated clozapine levels and clozapine toxicity. In some cases, toxicity is fatal with and without dose adjustments. In other cases, patients do not exhibit signs or symptoms of clozapine toxicity despite elevated levels. Patients with clozapine toxicity can be successfully managed by reducing the dose, clozapine cessation until infection resolves, or no change to dose with frequent drug monitoring. Alterations to clozapine doses should be done on a case-by-case basis and considerations should include that some patients may initially present asymptomatic from COVID-19 but still develop clozapine toxicity. Consider a dose reduction of 20-50% for all patients admitted for COVID-19 while being treated with clozapine. A clozapine level should be obtained in all patients admitted with COVID-19 while being treated with clozapine to assist in dose adjustments. Re-titration of clozapine should be conducted after resolution of COVID-19 symptoms, including if the patient developed an acute respiratory infection secondary to COVID-19. Clozapine toxicity can result if the medication is re-titrated during acute infection.

Question 1:
Which of the following is a dose-dependent related side effect of clozapine?

A. Weight gain
B. Seizures
C. NMS
D. Agranulocytosis
E. All of the above

Question 2:
Which of the following is generally considered a therapeutic clozapine level?

A. 750 mcg/L
B. 300 mg/L
C. 200 mcg/L
D. 450 mcg/L
E. 500 ng/L

Question 3:
What is the mechanism of clozapine toxicity in the setting of COVID-19?

A. CRP induced displacement of albumin-bound clozapine
B. Accumulation of Norclozapine
C. Cytokine inhibition of CYP1A2 metabolism
D. COVID-19 induced leukopenia
E. Tumor necrosis factor alpha binding of clozapine

Question 4:
A patient is admitted to the general medical floor for moderate COVID-19 infection with hypotension and confusion. The patient is currently taking clozapine 450 mg daily. Outpatient labs reveal a clozapine level of 388 mcg/L with clozapine/norclozapine level of 1.4. A clozapine level was obtained on admission and resulted at 943 mcg/L. Which of the following would you recommend?

A. Reduce clozapine dose to 300 mg
B. Order a confirmation clozapine level
C. Do not change clozapine dose
D. Hold clozapine during hospital admission

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