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Clozapine Serum Concentrations and Infectious Processes

Clozapine is a very effective antipsychotic often used in the treatment of schizophrenia.[1] Unfortunately, this medication can cause serious side effects such as delirium, myoclonus and seizures particularly when clozapine levels exceed the normal therapeutic range.[1] Clozapine levels can increase as a result of medication interactions, changes in nicotine and caffeine consumption, liver disease and overdoses.[1] In addition, clinicians must recognize infection, as a less widely known cause of increased clozapine levels.

Seventy percent of clozapine is metabolized by the CYP1A2 enzyme,[2] although CYP3A and UDP-glucuronosyltransferases are involved to a lesser degree.[3,4] Reports of elevated clozapine levels without proportional increases in the levels of the major metabolite, N-desmethylclozapine (norclozapine), suggest infectious processes interfere with the normal CYP1A2 metabolic conversion of clozapine. It is thought that during infection or inflammation, cytokines such as interferon-$_{\alpha\beta\eta\delta,}$ interleukin-$_{1}$, tumour necrosis factor and interleukin-$_{6}$ are released and may downregulate the activity of the CYP1A2 enzyme.[5] It should be noted that cytokine release can occur in the absence of infection through a clozapine mediated hypersensitivity reaction.[6]

Case reports of infectious processes causing toxic clozapine levels have emerged since the late 1990s. The following table provides a summary of these cases.

Author	Baseline Clozapine dose and levels	Infection Type	Clozapine dose(s) & level during infection	Interacting medications that could change clozapine levels	Comments
Raaska et al 2002 [7]	Clozapine 500 mg daily =1897 nmol/L clozapine	Bacterial pneumonia	Clozapine 500 mg daily = 6264 nmol/L clozapine.	Roxithromycin (macrolide antibiotic)	Clozapine dose decreased to 450 mg daily during infection. Clozapine levels returned to baseline once infection cleared.
De Leon, & Diaz FJ[8]	Clozapine 300 mg daily = 597 nmol/L clozapine and 367 nmol/L norclozapine	Respiratory infection	Clozapine 600 mg daily = 3810 nmol/L clozapine and 1447 nmol/L norclozapine	Olanzapine and propranolol (Timing indicates that use is unlikely to be a contributing factor to the increased clozapine levels)	During infection patient experienced “leg folding” (myoclonus) and sedation. Clozapine dose lowered to 400 mg/day. After infection cleared, myoclonus and sedation resolved.
Haack et al. 2003 [5]	Clozapine 600 mg daily. No baseline levels reported.	Infection suspected, no source identified.	Clozapine 600 mg daily = 7344 nmol/L clozapine and 2182 nmol/L norclozapine	Oxazepam	During infection patient suffered from flu-like symptoms, decreased blood pressure, weak pulse and extreme vomiting. Clozapine was stopped. Three weeks later flu symptoms resolved and clozapine level decreased to < 153 nmol/L

Haack et al. 2003 [5]	**Clozapine** 400 mg daily. No baseline levels reported.	**Pneumonia**	**Clozapine** 400 mg daily =5581 nmol/L clozapine and 1406 nmol/L norclozapine	**None**	**Clozapine stopped when** patient admitted to ER for vomiting and somnolence. Three days later pneumonia resolved and clozapine levels were within therapeutic range.
Haack et al. 2003 [5]	Clozapine 600 mg daily = 3231 nmol/L clozapine levels and 1518 nmol/L norclozapine. Since baseline levels high clozapine dose decreased to 500 mg	Viral Gastro-enteritis	Clozapine 500 mg daily = 7188 nmol/L clozapine and 1922 nmol/L norclozapine.	Unknown	Clozapine stopped. "The patient recovered without further investigation."[5]
Haack et al. 2003 [5]	Clozapine 500 mg daily. No baseline levels reported.	Pneumonia	500 mg daily= 2316 nmol/L clozapine and 903 nmol/L norclozapine. Clozapine dose then reduced to 300 mg daily. Next levels: clozapine 2800 nmol/L and norclozapine 869 nmol/L. Clozapine then stopped temporarily.	Clarythromycine (clarithromycin), fluoxetine, oxybutinin, promethazine	Jan 2000 to August 2000, "patient had two more bouts of pneumonia and clozapine plasma levels increased both time within a range of 3366-3672 nmol/L."[5]
Jecel J et al. 2005[9]	Clozapine 200 mg daily. No baseline levels reported.	Urinary Tract Infection	Clozapine 200 mg daily = 3262 nmol/L clozapine and 1160 nmol/L norclozapine. Then clozapine reduced to 100 mg daily.	Trimethoprim/ sulfamethoxazole (One dose only), mirtazapine	Episodes of aphasia, akinesia, and incoherent speech and gait disturbances noted during infection with concomitant increased clozapine levels. Once infection resolved and clozapine levels decreased (clozapine = 734 nmol/L and norclozapine =297 nmol/L) clozapine dose was increased back to 300 mg daily.

*****Clozapine level conversion 3.06x ng/ml = nmol/L*****

The previous cases illustrate that the infectious processes can more than double plasma clozapine levels, with a much lower impact on norclozapine. This is because the infection inhibits the conversion of clozapine to norclozapine via the CYP1A2 enzyme.[5] Normally in a patient on clozapine, the ratio of norclozapine to clozapine is approximately 0.8.[10] In the patients presented above, this ratio was reduced 2-3 fold during their infections.

Not all patients develop high clozapine levels during infections. The above case reports do however highlight the need to monitor for signs and symptoms of clozapine toxicity particularly when a patient develops respiratory infections e.g. pneumonia, and possibly other infections

It is suggested that if a patient with infection is sedated, delirious, has myoclonus and or seizures, that clozapine be withheld, or the daily dose reduced by 50% for the duration of the infection[11], depending on the acuity of the situation. Clozapine and norclozapine levels can be obtained if a patient has an infection and increased levels are suspected. However, as it may take days to obtain these results, it may be best to dose clozapine based on symptomatology rather than outdated levels.[8]

It is also important to remember that if clozapine is stopped for more than 48 hours, it must be re-started at a low dosage and titrated up to avoid adverse effects.

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