



Clinical Pharmacology & Toxicology Pearl of the Week

Clozapine

- ✓ Clozapine is an atypical antipsychotic most often reserved for use in patients who have treatment-resistant schizophrenia. It has a greater effect on negative symptoms and in patients with suicidal ideation than other antipsychotic drugs.
- ✓ Clozapine has the greatest association with causing weight gain (on average 30lbs in those on long-term therapy). It also causes hyperglycemia and insulin resistance in about 30-40% of patients, as well as hypertension and hyperlipidemia.

Clozapine Pharmacokinetics

- Absorption – Well absorbed with an oral bioavailability of 50% following first-pass metabolism
- Distribution – Highly variable volume of distribution (1.6 – 7 L/kg).
- Metabolism - Clozapine is extensively metabolized in the liver by CYP1A2 (major), CYP2D6 and CYP3A4. Most metabolites are inactive, although one (N-desmethylclozapine) has some limited activity at dopamine receptors.
- Elimination – elimination half-life of 12-14 hours, with a mix of renal (50%) and fecal (30%) elimination routes for metabolites.

Clozapine is associated with common adverse effects, such as:

- hypersalivation
- urinary incontinence
- constipation
- sedation.
- cholinergic rebound upon its cessation (should be tapered off if possible)

Clozapine is known to cause rare but serious adverse effects including:

- severe neutropenia
 - seizures
 - myocarditis
 - increased mortality in elderly patients with dementia-related psychosis
 - increased risk of orthostatic hypotension, bradycardia, and syncope
- ✓ In patients on clozapine, it is important to monitor a CBC, blood sugar & HbA1c% and a fasting lipid panel.
 - ✓ Maintaining a high degree of suspicion for drug-related adverse effects in patients on clozapine is essential.
 - ✓ Therapeutic drug monitoring with plasma levels of clozapine and norclozapine may aid in dose titration for patients with altered pharmacokinetics due to CYP enzyme genetic polymorphisms.

References:

1. Jann, MW, Grimsley, SR, Gray EC et al. Pharmacokinetics and Pharmacodynamics of Clozapine. Clin. Pharmacokinet.(1993)24:161.
2. Freudenreich O and McAvoy J. Guidelines for prescribing clozapine in schizophrenia(2019). In Marder, S. (Ed). UpToDate. Accessed online on Sept. 28, 2019.



The Calgary Clinical Pharmacology physician consultation service is available Mon-Fri, 9am-5pm. The on-call physician is listed in ROCA. Click [HERE](#) for clinical issues the CP service can assist with.



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