Clinical Pharmacology & Toxicology Pearl of the Week

~Tramadol~

- ✓ Tramadol inhibits the reuptake of serotonin and norepinephrine from the synaptic cleft; it also inhibits NMDA glutamatergic activity, thereby dampening neuroexcitation.
- ✓ Tramadol is not actually an opioid, rather it's metabolite, O-desmethyltramadol (M1), acts as a weak μ-opioid receptor agonist – **tramadol relies on liver metabolism to have any opioid properties.**

Serotonergic activity of Tramadol

- ✓ Tramadol itself acts as an **SNRI** and is structurally very similar to venlafaxine (figure 1)
- ✓ When combined with other serotonergic medication, serotonin toxicity is possible
- ✓ Sudden discontinuation of tramadol can present with antidepressant discontinuation syndrome

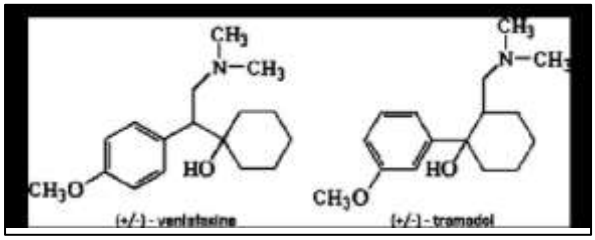

Figure 1: Structural similarity between tramadol and venlafaxine

Metabolism of Tramadol

- ✓ Tramadol is a substrate of cytochrome P450 enzymes CYP3A4 and CYP2D6. It is subject to variable metabolism leading to unpredictable clinical effects, and is also commonly affected by drug-drug interactions
- ✓ Tramadol induces its own metabolism, as it is both a substrate and inducer of CYP2D6
- ✓ Tramadol is variably metabolized into two metabolites:
  - active metabolite O-desmethyltramadol (M1), which occurs via CYP2D6
  - inactive N-desmethyltramadol (M2), which occurs via CYP3A4

Opioid effects of Tramadol Metabolites

- ✓ Tramadol is similar to codeine in that it requires activation into its opioid metabolite to have opioid properties.
- ✓ M1 (O-desmethyltramadol) has higher μ-opioid receptor affinity than tramadol itself. M1 is released into circulation following metabolism and acts upon central μ-opioid receptors, providing analgesic and euphoric properties that can lead to physiologic dependence and addiction similar to all other opioids.
- ✓ Another metabolite, M5 (N,O-di-desmethyltramadol), is also active at μ-opioid receptors, but less so than M1.

Genetic Polymorphisms and Variable Metabolism

- ✓ Due to different CYP-2D6 genotypes, people variably metabolize tramadol into its active metabolite, M1
- ✓ This leads to an **unpredictable** mix of SNRI and opioid effects in patients
  - Ultra-rapid metabolizers
    - Some people are ultra-rapid metabolizers of tramadol (By the same CYP2D6 polymorphism resulting in codeine ultra-rapid metabolism)
    - Death and life threatening respiratory depression have occurred following a single dose of tramadol in children
    - Risk of infant respiratory depression in breast-feeding if mother or child are ultra-rapid metabolizers
  - Poor metabolizers
    - In poor metabolizers, people may experience little, or no analgesic activity as the M1 metabolite cannot be created. (By the same CYP-2D6 polymorphism resulting in poor codeine metabolism and little to no analgesic activity).

Summary:

Tramadol can be likened to a mix of codeine and venlafaxine in unpredictable quantities as it depends on an individual's genetic makeup as to how much SNRI vs. opioid effect the drug has.

It can be dangerous in those with ultra-rapid metabolism, and can lead to serotonin syndrome when combined with other serotonergic medications. It may also cause hypoglycemia.

Caution must be exercised when prescribing this complex and unpredictable medication.

References:

1. Brunton L, Hilal-Dandan R, Knollmann B, editors. Goodman & Gilman's The Pharmacological Basis of Therapeutics. 13th ed. New York: McGraw Hill Medical; c2018
2. Nelson L, Lewin N, Howland M, Hoffman R, Goldfrank L, Flomenbaum N, editors. Goldfrank's Toxicologic Emergencies. 9th ed. New York: McGraw Hill Medical; c2011
3. Stamer UM, Musshoff F, Kobilay M, Madea B, Hoeft A, Stuber F. Concentrations of Tramadol and O-desmethyltramadol enantiomers in different CYP2D6 genotypes. Clin Pharmacol Ther 2007 March;82(1): 41-47
4. Lexicomp Online, Pediatric and Neonatal Lexi-Drugs Online, Hudson, Ohio: Wolters Kluwer Clinical Drug Information, Inc.; 2013; April 15, 2013.
5. Gong L, Stamer U, Tzvetkov M, Altman A, Klein T. PharmGKB summary: tramadol pathway. Pharmacogenet Genom. 2014 July;24(7): 374-380

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.

The Poison and Drug Information Service (PADIS) is available 24/7 for questions related to poisonings. Please call 1-800-332-1414, and select option 1.