Clinical Pharmacology & Toxicology Pearl of the Week

Mechanisms of drug-drug interactions

Drug-drug interactions are quite common and often predictable

Interactions more often occur via pharmacokinetics interactions with another xenobiotic, and less commonly via pharmacodynamic mechanisms that lead to synergistic or antagonistic mechanisms of action

For an introduction to pharmacokinetics, please refer to this recent pearl of the week

Micromedex or Lexicomp are accessible on AHS computers, it is recommended that medications are reviewed using these tools to verify drug-drug interactions prior to prescribing

Mechanisms that affect absorption

- ✓ Xenobiotics that alter the pH of the stomach or intestine can alter the ionization status of other xenobiotics, increasing or decreasing their absorption
- ✓ Xenobiotics that decrease gastric emptying rate will delay absorption of other xenobiotics, leading to lower peak serum concentrations and delayed effect
  - Ex: Antimuscarinic medications, salicylates, ETOH, opioids
- ✓ Xenobiotics that can chelate or bind to other xenobiotics will decrease their absorption
  - Ex: Calcium or Iron supplements with tetracycline antibiotics
- ✓ p-glycoprotein (ABCB-1) is found on the luminal membrane in the intestine and functions to 'pump' drugs out of enterocytes and back into the lumen of the intestine
  - Important p-glycoprotein substrates: colchicine, cyclosporine, dabigatran, digoxin, diltiazem, sirolimus
  - p-glycoprotein inhibitors will **increase** the concentration of p-glycoprotein substrates in the body
    - Ex: amiodarone, diltiazem, macrolides, PPIs, ketoconazole, sertraline, duloxetine
  - p-glycoprotein inducers will **decrease** the concentration of p-glycoprotein substrates in the body
    - Ex: carbamazepine, dexamethasone, phenytoin, rifampicin, trazodone, prazosin, St. John's Wart

Distribution

- ✓ p-glycoprotein is also found on the blood-brain-barrier as an efflux transporter out of the CNS
- ✓ p-glycoprotein inhibition can increase the CNS concentration of xenobiotics
  - This has been manipulated to increase chemotherapeutic, anti-retroviral, and anti-epileptic concentrations within the CNS
- ✓ Xenobiotics that change serum pH can alter distribution of drugs into lipophilic tissues (such as the brain)
  - Ex: Lactic acidosis from metformin overdose will increase penetration of salicylate co-ingested into the CNS

Metabolism

- ✓ Xenobiotics with shared metabolic pathways can competitively inhibit each other's metabolism if enzymes become saturated, resulting in decreased metabolism
  - Ex: Ethanol and methanol competing for ADH
- ✓ Inhibition can also be irreversible if the xenobiotic forms a stable complex with a metabolic enzyme
  - Ex: MAOIs binding to MAO
  - Ex: itraconazole, clarithromycin, diltiazem, fluoxetine, anti-retrovirals and verapamil binding to CYP 3A4
- ✓ Xenobiotics can induce expression of CYP450 enzymes, resulting in increased metabolism of xenobiotics metabolized by these CYP enzymes (or even themselves)
  - This occurs through transcriptional gene activation by binding to pregnane X receptor (PXR) and constitutive androstane receptor (CAR) (upstream transcriptional activators).

- Is usually non-specific, inducing multiple CYP enzymes
    - Ex: barbituates, carbamazepine, rifampin, chloroxyquinolone, artemisininin, steroids

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Induction of CYP450 enzymes takes time since the cells need to transcribe and translate new proteins. Maximal effect takes one to two weeks

Elimination

- ✓ Xenobiotics that alter renal perfusion and blood flow can decrease elimination of xenobiotics and their metabolites
    - Ex: ACE-inhibitors, Angiotensin Receptor Blockers, and NSAIDS decrease renal perfusion, decreasing clearance of renally cleared xenobiotics such as digoxin, metformin, sotalol, and vancomycin
- ✓ Xenobiotics that alter gut microbiomes (antibiotics) can decrease microbial cleavage of glucuronidated metabolites that are eliminated in the bile, decreasing re-absorption of these xenobiotics
    - As such, a higher dose may be required to continue to achieve therapeutic efficacy while undergoing antimicrobial therapy
    - Ex: Phenytoin, estrogens, diclofenac

Xenobiotic mechanism of action

- ✓ Xenobiotics that share mechanisms of action or have similar effects can result in a synergistic effect
    - Ex: methotrexate, sulfamethoxazole and trimethoprim all inhibit purine synthesis. Co-prescription of septra with methotrexate increases potential toxic effects of methotrexate.
    - Ex: combining anti-platelet agents with heparin-based anticoagulants increases risk of bleeding
    - Ex: combining serotonin re-uptake inhibitors with serotonin releasing xenobiotics (ex: cocaine) or with xenobiotics that inhibit serotonin breakdown (Ex: MAOIs, St. John's Wart) increases the risk of serotonin toxicity.

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.

References:

1. Lewis S. Nelson et al, Goldfrank's Toxicologic Emergencies. 11th ed. New York: McGraw Hill Medical; c2019
2. Buxton IO. Pharmacokinetics: The Dynamics of Drug Absorption, Distribution, Metabolism, and Elimination. In: Brunton LL, Hilal-Dandan R, Knollmann BC. eds. *Goodman & Gilman's: The Pharmacological Basis of Therapeutics, 13e* New York, NY: McGraw-Hill; http://accesspharmacy.mhmedical.com.ca/content.aspx?bookid=2189&sectionid=166182905. Accessed December 27, 2019.
3. Miller DS, Bauer B, Hartz AM. Modulation of P-glycoprotein at the blood-brain barrier: opportunities to improve central nervous system pharmacotherapy. *Pharmacol Rev*. 2008;60(2):196–209. doi:10.1124/pr.107.07109