Clinical Pharmacology & Toxicology Pearl of the Week

~ Grapefruit Juice & Oral Medication Toxicity ~

Case:

- ✓ A 50 yo female presents feeling unwell and "sick" for the last few days – she is found to be tachycardic, hypotensive, and reports a history of nausea, vomiting, and diarrhea over the first 1-2 days of illness which has now begun to resolve.

- ✓ Workup reveals new pancytopenia, as well as a new acute kidney injury (Cr baseline 60s, today 120).

- ✓ Her only past medical history is gout for which she has recently initiated urate lowering-therapy with allopurinol and concurrently been placed on prophylactic colchicine at 0.6 mg PO daily – she has been taking these medications reliably for the past month.

- ✓ Your team suspects colchicine toxicity – however, the patient adamantly denies an overdose history or any misuse of her medications.

- ✓ While admitted, she asks the nurse if the hospital has grapefruit juice as she likes to drink at least 2 glasses/day for its health benefits.

Background:

- ✓ Grapefruit (along with several other related citrus fruits) has been identified to interact with numerous prescribed medications, resulting in increased adverse effects.

- ✓ Drugs that interact with grapefruit, in general, all carry the following similar traits (***For a full list of relevant grapefruit-drug interactions, please see Bailey et al. 2013***)
    - Orally (PO) administered
    - Low-to-intermediate absolute bioavailability at baseline
    - Metabolized by the CYP P450 3A4 enzyme system

- ✓ CYP3A4 is found both within the epithelial cells lining the GI tract, as well as within hepatocytes - drugs metabolized by CYP3A4 and administered orally (PO) therefore undergo two metabolic "hits" prior to reaching systemic circulation.

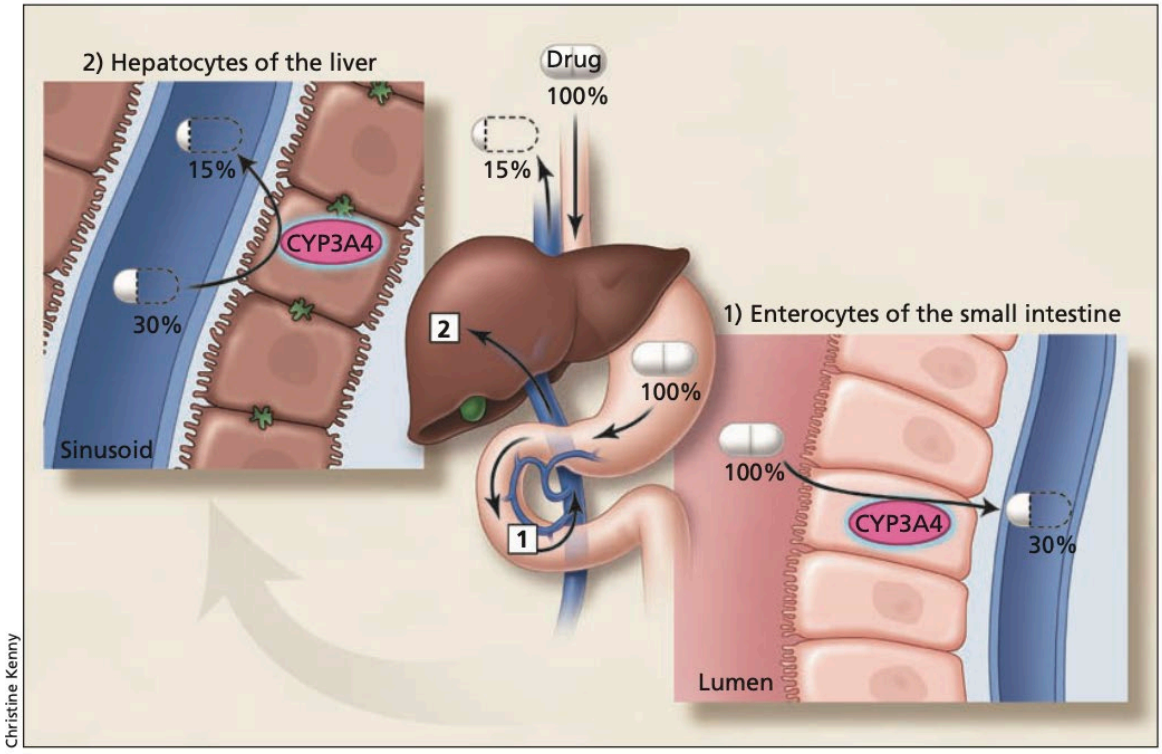

Image from Bailey et al. (2013)

- ✓ Grapefruit's interaction is due to the inhibitory effect of "furanocoumarins" found in grapefruit products – furanocoumarins are metabolized by CYP3A4 to reactive intermediates that then themselves can inhibit the CYP3A4 system within the GI epithelial cells.

- ✓ Furanocoumarin inhibition of GI epithelial cell CYP3A4 therefore affects the bioavailability of these drugs, leading to potential increased serum concentrations and adverse effects as a result.

Factors Determining Clinical Significance:

- ✓ *Drug Oral Bioavailability*
  - Drugs with a low baseline oral bioavailability (<10-30%) have a greater chance at clinically significant changes to drug concentrations, and therefore clinical effects.
  - Drugs with a high baseline bioavailability (>70%) are unlikely to have their serum concentrations impacted, and therefore clinical effects are expected to be marginal.

- ✓ *Grapefruit Consumption Patterns*
  - A single consumption of a usual amount of grapefruit juice (200-250 mL) has the potential for significant pharmacokinetic interaction up to 24 hours and more.
    - Lundahl et al. (1995) examined the effect of a single 200 mL consumption of grapefruit juice on felodipine XR pharmacokinetic parameters, with drug administration at 1, 4, 10, and 24 hours after grapefruit consumption.
    - While effects were greatest within 4 hours of grapefruit exposure, an increased Cmax of felodipine XR was seen up to 24 hours.
    - There were no clinical differences documented as a result.
  - Frequent and repeated ingestion of grapefruit (either the juice or whole grapefruit) has also been shown to demonstrate increased CYP3A4 inhibition compared to a single ingestion alone.

- Interestingly, a single ingestion of more than a usual amount of grapefruit juice (200-250 mL) was not identified to impact the pharmacokinetic parameters of felodipine compared to a usual single ingestion.

✓ *Patient Risk or "Vulnerability"*
- CYP3A4 Levels
  - The level of CYP3A4 in GI epithelial cells varies between individuals, therefore impacting the effect of CYP3A4 inhibition by furanocoumarins.
    - A study by Lown et al. (1997) examining felodipine concentrations after a single-serving of grapefruit juice ranged from 0 to 8-fold; biopsies of the small intestine in this group of patients demonstrated variable CYP3A4 levels.
- CYP3A4 Function
  - Genomic differences between patients may also result in decreased or increased function CYP3A4, which could impact the effect of inhibition.
  - Additionally, patients taking other CYP3A4 altering substances may have more unpredictable response to furanocoumarin interaction.
- Patient Age
  - Elderly patients are identified to be both the patients who consume grapefruit products AND who receive the most prescription drugs.
  - Elderly patients may also be more clinically affected by changes to drug concentration.

Relevant Clinical Examples:

ADVERSE EFFECT	***DRUG***	***GRAPEFRUIT CONSUMED***	***REFERENCE***
Torsade de Pointes	Amiodarone	1-1.5 L/d on a regular basis of grapefruit juice.	*Agosti 2012*
	Quinine	"High volume" in days preceding drug administration.	*Hermans 2003*
Complete Heart Block	Verapamil	"High volume" in days preceding drug administration.	*Pillai 2009*
Rhabdomyolysis	Atorvastatin	1-2 glasses/d for 5 days of grapefruit juice.	*Mazokopakis 2008; Karch 2004*
	Simvastatin	1 whole grapefruit/d for 2 weeks.	*Dreier 2004*
Nephrotoxicity	Tacrolimus	1.5 kg of marmalade eaten over the preceding 1 week.	*Peynaud 2007*
Myelotoxicity	Colchicine	1 L grapefruit juice/d for preceding 2 months.	*Goldbart 2000*
Venous Thrombosis	Ethinylestradiol	1 whole grapefruit/d for preceding 3 days.	*Grande 2009*

Table adapted from Bailey et al. (2013).

Case Resolution:

✓ You learn that over the past year, the patient has been consuming approximately 400-500 mL of grapefruit juice / day and suspect that as a result, she manifested a clinically significant increase in serum colchicine concentrations resulting in toxicity.

- ✓ She is monitored in the ICU setting for the initial 24-48 hours due to the risk of potential CV collapse, and luckily survives with appropriate supportive care.

The Clinical Pharmacology physician consultation service is available Mon-Fri, 8am-5pm. The on-call physician is listed in ROCA on the AHS Insite page. Clinical Pharmacology consultations are also available through the Netcare e-referral process and through Calgary Zone Specialist Link. Click HERE for more details.

The Poison and Drug Information Service (PADIS) is available 24/7 for questions related to poisonings. Please call 1-800-332-1414 (AB and NWT) or 1-866-454-1212 (SK).

References / Resources

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