



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.

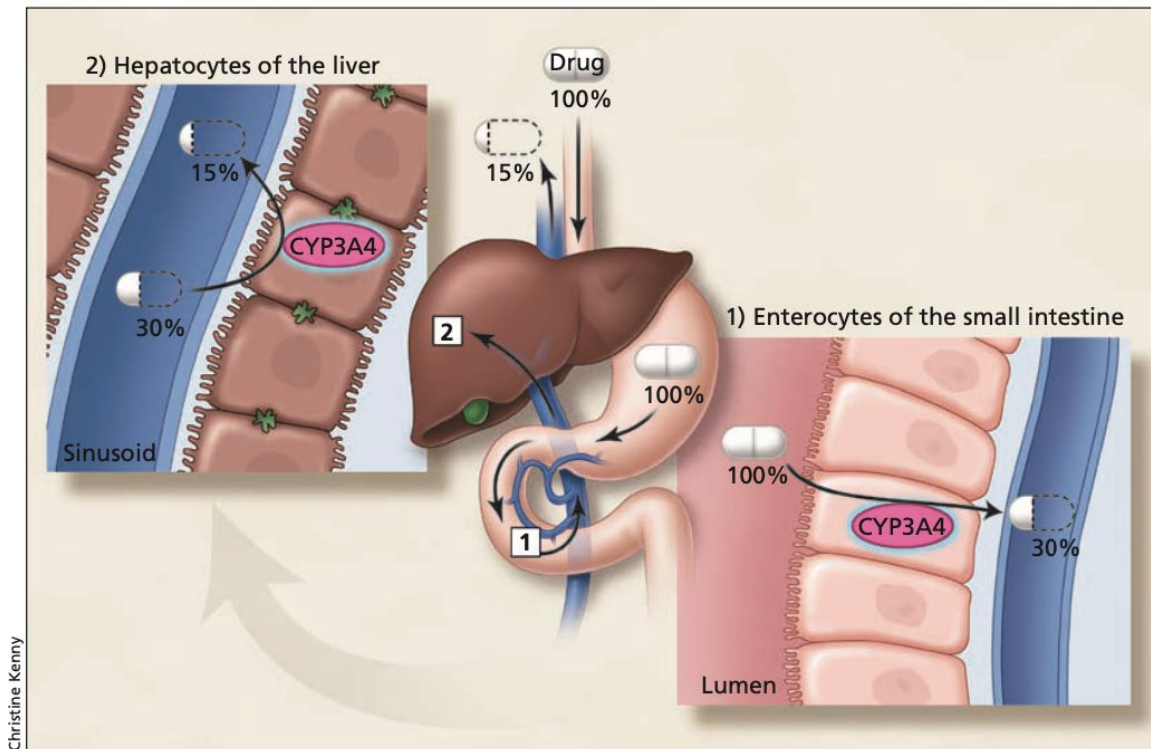


Image from Bailey et al. (2013)

- ✓ 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 C_{max} 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.	<i>Agosti 2012</i>
	Quinine	“High volume” in days preceding drug administration.	<i>Hermans 2003</i>
Complete Heart Block	Verapamil	“High volume” in days preceding drug administration.	<i>Pillai 2009</i>
Rhabdomyolysis	Atorvastatin	1-2 glasses/d for 5 days of grapefruit juice.	<i>Mazokopakis 2008;</i> <i>Karch 2004</i>
	Simvastatin	1 whole grapefruit/d for 2 weeks.	<i>Dreier 2004</i>
Nephrotoxicity	Tacrolimus	1.5 kg of marmalade eaten over the preceding 1 week.	<i>Peynaud 2007</i>
Myelotoxicity	Colchicine	1 L grapefruit juice/d for preceding 2 months.	<i>Goldbart 2000</i>
Venous Thrombosis	Ethinylestradiol	1 whole grapefruit/d for preceding 3 days.	<i>Grande 2009</i>

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.

References / Resources

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11. Karch AM. The grapefruit challenge: the juice inhibits a crucial enzyme, with possibly fatal consequences. *Am J Nurs*. 2004;104:33-5.
12. Dreier JP et al. Statin-associated rhabdomyolysis triggered by grapefruit consumption. *Neurology*. 2004;62:670.
13. Peynaud D et al. Tacrolimus severe over-dosage after intake of masked grapefruit in orange marmalade. *Eur J Clin Pharmacol*. 2007;63:721-2.
14. Goldbart A et al. Near fatal acute colchicine intoxication in a child: a case report. *Eur J Pediatr*. 2000;159:895-7.
15. Grande LA et al. Attention grapefruit! *Lancet*. 2009;373:1222.

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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). Information about our outpatient Medical Toxicology Clinic can be found in [Alberta Referral Directory](#) (ARD) by searching “Toxicology” from the ARD home page.

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