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HEALTH AND DRUG ALERTS

Grapefruit juice: potential drug interactions

Reason for posting: Grapefruit juice interacts with a number of medications. This unusual discovery was made serendipitously in 1989 during an experiment designed to test the effect of ethanol on a calcium-channel blocker.¹ The observed response was later determined to be due to the grapefruit juice delivery vehicle rather than the alcohol. In the past decade, the list of drug interactions with grapefruit juice has expanded to include several classes of medication, precipitating a recent advisory from Health Canada.²

The interaction: As little as 250 mL of grapefruit juice can change the metabolism of some drugs.³ This drug-food interaction occurs because of a common pathway involving a specific isoform of cytochrome P450 — CYP3A4 — present in both the liver and the intestinal wall. Studies suggest that grapefruit juice exerts its effect primarily at the level of the intestine.⁴

After ingestion, a substrate contained in the grapefruit binds to the intestinal isoenzyme, impairing first-pass metabolism directly and causing a sustained decrease in CYP3A4 protein expression.⁵ Within 4 hours of ingestion, a reduction in the effective CYP3A4

concentration occurs, with effects lasting up to 24 hours.⁶ The net result is inhibition of drug metabolism in the intestine and increased oral bioavailability. Because of the prolonged response, separating the intake of the drug and the juice does not prevent interference.

Individuals express CYP3A4 in different proportions, those with the highest intestinal concentration being most susceptible to grapefruit juice-drug interactions.⁵ An effect is seen with the whole fruit as well as its juice, so caution should be exercised with both.⁷ The precise chemical compound in grapefruit that causes the interaction has not been identified. There is no similar reaction with

orange juice, although there is some suspicion that “sour oranges” such as the Seville variety, may have some effect.⁸ A recent study, however, that tested the known interference of grapefruit juice with cyclosporine showed no similar effect with Seville oranges.⁹

There is some interest in the potential therapeutic benefit of adding grapefruit juice to a drug regimen to increase oral bioavailability.³ The limitation is the individual variation in patient response. However, if the chemical that causes grapefruit’s CYP3A4 inhibition is elucidated, there may be an opportunity to modulate that pathway in a controlled fashion.

Canadian Adverse Reaction Newsletter Bulletin canadien des effets indésirables

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Table 1: Possible interactions between grapefruit juice (GJ)* and drugs metabolized by CYP3A4

Drug class	Drug	Possible adverse effects	Increased oral bioavailability	Management
Antiarrhythmics	Amiodarone	Arrhythmias	Yes	Avoid GJ
	Quinidine	None	No	None
Antibiotics	Clarithromycin	None	No	None
Antihistamines	Terfenadine	Arrhythmias, prolonged Q-T interval	Yes	Avoid GJ
Anxiolytics	Buspirone	Decreased psychomotor performance, increased sedation	Yes	Avoid GJ
	Diazepam	"	Yes	Avoid GJ
	Midazolam	"	Yes	Avoid GJ
	Triazolam	"	Yes	Avoid GJ
Calcium-channel blockers	Amlodipine	Tachycardia, hypotension	Yes	Avoid GJ
	Felodipine	"	Yes	Avoid GJ
	Nifedipine	"	Yes	Avoid GJ
	Nimodipine	"	Yes	Avoid GJ
	Diltiazem	None	No	None
	Verapamil	None	No	None
Corticosteroids	Ethinyl estradiol	Unknown	Yes	Monitor for side effects
	Progesterone	Unknown	Possible	Monitor for side effects
	Prednisone	None	No	None
HMG-CoA reductase inhibitors	Atorvastatin	Myopathy, headache, rhabdomyolysis	Yes	Avoid GJ
	Cerivastatin	"	Possible	Monitor for side effects
	Lovastatin	"	Yes	Avoid GJ
	Pravastatin	"	Yes	Avoid GJ
	Simvastatin	"	Yes	Avoid GJ
HIV protease inhibitors	Saquinavir	Unknown	Yes†	Monitor for side effects
Immunosuppressants	Cyclosporine	Renal/hepatic dysfunction, increased immunosuppression	Yes	Avoid GJ
	Tacrolimus		Yes	Avoid GJ
Neuropsychiatric	Carbamazepine	Drowsiness, ataxia, nausea	Yes	Avoid GJ
	Clomipramine	Drowsiness, respiratory depression	Yes	Monitor for side effects
	Phenytoin	None	No	None
Other	Carvedilol	Bradycardia, hypotension	Possible	Monitor for side effects
	Metadone	Respiratory depression, hypotension	Possible	Monitor for side effects
	Sildenafil	Headache, flushing, dyspepsia	Possible	Monitor for side effects
	Theophylline	None	No	None
	Warfarin	None	No	None

*Grapefruit juice and the whole fruit.

†Clinical significance unknown.

What to do: Much of the data obtained on grapefruit juice–drug interactions involved measuring serum drug concentrations in small numbers of healthy volunteers. Because of the limited data and only occasional case reports,¹⁰ it is difficult to quantify the clinical significance for individual patients. One may assume that the interaction occurs primarily with oral medicines, and only with those that share the CYP3A4 metabolism pathway, with the consequence being increased oral bioavailability, higher serum drug concentrations and associated adverse effects.

Physicians should review medication lists often, with the goal of warning patients about adverse interactions. A list of medicines with which patients should not consume grapefruit is provided in Table 1.^{3,11,12} In the case of several medications that share the

CYP3A4 metabolism pathway, but for which a clinical effect has not been elucidated or is theoretical, patients should be advised to consume grapefruit cautiously and be monitored for toxicity.

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