Management of Grapefruit-Drug Interactions

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Grapefruit is a healthy addition to a well-balanced diet. However, the fruit has been shown to affect the metabolism of many medications, increasing the risk of toxicity and adverse effects. Characteristics of oral medications that may interact with grapefruit include extensive metabolism through the intestinal cytochrome P450 3A4 system, low bioavailability, and a narrow therapeutic index. Prominent medications known to interact with grapefruit include statins, antiarrhythmic agents, immunosuppressive agents, and calcium channel blockers. There are equally effective alternatives to these drug classes that do not have the potential to interact with grapefruit. These alternative drugs may be substituted if a patient experiences or is at risk of a grapefruit-drug interaction. Patients also may choose to exclude grapefruit from their diets and consume other fruits, including other types of citrus, to avoid an interaction. (Am Fam Physician 2006;74:605-8, 611. Copyright © 2006 American Academy of Family Physicians.)

▶ **Patient information:** A handout on medicine interactions with grapefruit, written by the authors of this article, is provided on page 611.

Grapefruit is a citrus fruit that is low in calories; rich in vitamin C, potassium, and dietary fiber; and has been a recommended fruit of the American Heart Association's "Healthy Heart Campaign."[1] The authors of a study[2] that used grapefruit juice to mask the taste of ethanol inadvertently discovered an interaction between grapefruit and the calcium channel blocker felodipine (Plendil). They observed that patients who consumed grapefruit juice had felodipine plasma concentrations two to three times higher than normal levels.[2]

The discovery of this and other clinically significant interactions may have caused health care professionals to hesitate before universally recommending grapefruit as part of a healthy diet. Because grapefruit-drug interactions exist, strategies should be devised to manage potential interactions. A patient may choose to exclude grapefruit from his or her diet and substitute other fruits, including any other citrus.[3] However, if the patient wishes to continue to consume grapefruit products, an alternate medication that does not have the potential to interact with grapefruit may be prescribed.

The most significant characteristic that determines drug interaction with grapefruit is metabolism by the intestinal cytochrome P450 3A4 system.

MECHANISM OF INTERACTION

The characteristics of medications that interact with grapefruit are well defined. The most significant of these characteristics is metabolism by the intestinal cytochrome P450 3A4 (CYP 3A4) system. CYP 3A4 is found in the liver and intestinal tract. Intestinal CYP 3A4 concentration can be decreased by 47 percent within four hours of grapefruit consumption.[4] One study[5] has shown that the interaction persists for up to 72 hours; therefore, it would be prudent to avoid grapefruit products for 72 hours before taking a medication with which they may interact.

Another study[6] reported that consuming 8 oz of grapefruit juice can inhibit intestinal CYP 3A4 concentration for 24 to 72 hours. Therefore, separating the times of medication administration and grapefruit consumption is not a plausible solution.[5,6] It is important to note that because of genetic polymorphism, persons have varying amounts of intestinal CYP 3A4; consequently, the extent of an interaction is not predictable from patient to patient.[7,8]

The substance or substances in grapefruit that inhibit intestinal CYP 3A4 have not been identified. In addition, grapefruit may decrease the intestinal transport of drugs into the circulation.[7] Because intestinal

SORT: KEY RECOMMENDATIONS FOR PRACTICE

Clinical recommendation	*Evidence rating*	*References*	*Comments*
Patients should discontinue grapefruit consumption for 72 hours before use of a drug that may interact with it.	C	5, 6	The potential for a grapefruit-drug interaction persists for up to 72 hours according to one study.[5]
Potential grapefruit-drug interactions cannot be avoided by separating times of medication administration and grapefruit consumption.	C	5, 6	Studies have shown that consuming 8 oz of grapefruit juice may decrease the concentration of intestinal cytochrome P450 3A4 by 47 percent for 24 to 72 hours.

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, see page 542 or http://www.aafp.org/afpsort.xml.

CYP 3A4 is affected, the interaction will only occur with oral formulations. Studies of the intravenous form of drugs that are substrates of hepatic CYP 3A4 and have the potential to interact with grapefruit failed to demonstrate any effect on plasma concentration.[4]

Medications metabolized by intestinal CYP 3A4 that have a low oral bioavailability or a narrow therapeutic index are more likely to have clinically significant interactions with grapefruit products.[9] Because medications metabolized extensively by intestinal CYP 3A4 generally have low oral bioavailability, and because grapefruit inhibits this metabolic pathway, higher plasma concentrations of these medications will result. Furthermore, if the medication has a narrow therapeutic index, small increases in plasma concentration may cause drastic increases in therapeutic or adverse effects.[9]

MANAGEMENT

When considering how to manage grapefruit-drug interactions, a physician should first decide if the interaction is clinically relevant. A number of medications (e.g., angiotensin receptor blockers, buspirone [BuSpar], estrogens, fexofenadine [Allegra], itraconazole [Sporanox], sildenafil [Viagra], triazolam [Halcion], warfarin [Coumadin]) reportedly or theoretically interact with grapefruit. However, many of these interactions have not been proven clinically significant, or inconsistent data exist.[10-18] *Table 1*[9,19-30] describes medication classes that have had documented, clinically significant interactions with grapefruit products, and possible alternative therapies for these drugs.

Patients should avoid grapefruit products for 72 hours before taking a drug with which they may interact.

The importance of clearly understanding possible interactions between drugs and grapefruit products is becoming more evident. The manufacturers of cyclosporine (Sandimmune, Neoral) and simvastatin (Zocor) have gone so far as to place warnings on their drugs' package inserts.[25,31,32]

Members of various family medicine departments develop articles for "Clinical Pharmacology." This is one in a series coordinated by Allen F. Shaughnessy, Pharm.D., and Andrea E. Gordon, M.D., Tufts University Family Medicine Residency, Malden, Mass.

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TABLE 1
Grapefruit-Drug Interactions and Alternative Therapies

Drug class	*Drugs potentially affected by grapefruit*	*Effects of interaction*	*Alternative treatments*
Antiarrhythmics	Amiodarone (Cordarone), disopyramide (Norpace), quinidine	Increased plasma concentrations of amiodarone may cause thyroid or pulmonary toxicity, liver injury, QTc prolongation, proarrhythmic disorders, and bradycardia.[19] Increased plasma concentration of quinidine and disopyramide may be cardiotoxic causing torsades de pointes.[9,20]	Digoxin (Lanoxin), diltiazem (Cardizem), verapamil (Calan) Beta blockers
Calcium channel blockers	Felodipine (Plendil), nicardipine (Cardene), nifedipine (Procardia), nimodipine (Nimotop), nisoldipine (Sular)	Increased plasma concentration may lead to flushing, peripheral edema, headaches, tachycardia, symptomatic hypotension, and myocardial infarction in rare cases.[9]	Amlodipine (Norvasc), diltiazem (Cardizem), verapamil (Calan)
Statins	Atorvastatin (Lipitor), lovastatin (Mevacor), simvastatin (Zocor)	Increased plasma concentration may cause headaches, gastrointestinal complaints, hepatic inflammation, and myopathies (e.g., rhabdomyolysis).[21-24]	Fluvastatin (Lescol), pravastatin (Pravachol), rosuvastatin (Crestor) Fibric acids, nicotinic acid, or bile acid sequestrants
Immunosuppressants	Cyclosporine (Sandimmune, Neoral), tacrolimus (Prograf)	Increased drug exposure without effects on peak concentration may cause increased adverse events or toxicity evidenced by renal toxicity, hepatic toxicity, and increased immunosuppression.[25-29]	No alternatives available
Protease inhibitors	Saquinavir (Fortovase)	Increased plasma concentrations may cause increased side effects such as headache, fatigue, insomnia, and anxiety.[30]	Amprenavir (Agenerase), atazanavir (Reyataz), fosamprenavir (Lexiva), indinavir (Crixivan), lopinavir/ritonavir (Kaletra), nelfinavir (Viracept), ritonavir (Norvir)

Information from references 9 and 19 through 30.

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