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Grapefruit and medications may be a deadly mix- An overview

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Abstract

Grapefruit juice, which is widely consumed for its positive health benefits, can have severe, sometimes fatal, interactions with drugs. The co-administration of drugs with grapefruit juice can markedly elevate drug bioavailability, and can alter pharmacokinetic and pharmacodynamic parameters of the drug. In some instances, the interaction may have a beneficial effect by increasing drug efficacy or diminishing potential side effects. The mechanism for this interaction is the inhibition of cytochrome P-450 3A4 in the small intestine, resulting in a significant reduction of drug pre-systemic metabolism. An additional mechanism is, presumably, the inhibition of P-glycoprotein, a transporter that carries drug from the enterocyte back to the gut lumen, resulting in a further increase in the fraction of drug absorbed. Usual grapefruit intake inhibits only gut CYP3A; not liver CYP3A. Therefore, grapefruit does not normally affect medications given intravenously. Recent review found that more than 85 drugs can be affected by grapefruit juice. One whole grapefruit or 200 mL (about seven ounces) of juice can be enough to cause a clinically important interaction. The data available so far, concerning this interaction and its clinical implications, are reviewed in this article. By reviewing this in the future it will create awareness. There by optimal drug therapy can be achieved.

Keywords: Grapefruit, drug interaction, pharmacokinetics, bioavailability

Introduction

Many people have the mistaken notion that being natural, all herbs and foods are safe. This is not so. Very often, herbs and foods may interact with medications normally taken that result in serious adverse reactions. Drug interactions have the potential to affect the way the body processes and metabolizes a drug (pharmacokinetics [PK]) and increase or decrease expression of the drug's effects (Pharmacodynamics [PD])[1,2]. Drugs can interact with other drugs or they can interact with food, nutrients, or dietary supplements. Since these dietary products share many characteristics with drugs, including similar absorption sites in the intestine, they have the ability to alter physiological processes and the potential for toxicity in high doses[2,3].

Grapefruit is low in calories and high in vitamin C, potassium, and dietary fiber and, as such, is frequently consumed for its health benefits[4-9] Grapefruit consumption has been associated with weight loss and improved lipid levels[10] Grapefruit's popularity has increased since its inclusion in fad diets in the 1930s[9] and grapefruit juice is now a commonly consumed beverage in North America[4].

Mechanism of grape fruit–drug interaction

Grapefruit juice contains furanocoumarins (such as 6,7-dihydroxybergamottin)[11], which can cause irreversible inhibition of the cytochrome P450 enzyme, CYP3A4, mainly in the small intestine[12]. Since CYP3A4 is involved in the metabolism of around 50% of drugs, wide variety of drugs can be affected by the consumption of grapefruit juice and resulted reduction in the pre-systemic metabolism of these drugs, which increases their systemic exposure, sometimes by more than 70%[13]. Because inhibition of CYP3A4 is irreversible, it can last for longer than three days after ingestion of grapefruit juice, until new enzyme has been synthesized in the gut wall[2]. Both the consumption of fruit and fruit juice can cause the interaction[14]. It will be greater in regular consumption. The clinical consequences can vary from an asymptomatic increase in drug concentrations to life threatening events.
A second mechanism involves the inhibition of a member of the influx transporter protein family (organic anion transporter polypeptide; OATP) by grapefruit[15]

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Flavonoids such as naringin and hesperidin have been implicated in the mechanism of OATP inhibition. The net effect is reduced bioavailability of the drug, with a decrease in its systemic and tissue concentrations and thus a decrease in its efficacy. In contrast to the effect of grapefruit juice on CYP3A4, the inhibition of OATPs shows a clear volume (dose)-response association, which is competitive in nature, with inhibition lasting about four hours. Thus, a simple way to avoid this interaction is to have a four hour gap between the intake of grapefruit juice and drug administration[16].

The effect will vary depends on the bioavailability of the drug, the intrinsic level of expression of CYP3A4 individual, frequency of grapefruit juice consumption[17].

Table1: Medications that should be avoided with grapefruit

Amiodarone (Cordarone)[8]
Astemizole (Hismanal)[5, 9]
Atorvastatin (Lipitor)
Budesonide (Entocort)[8]
Buspirone (Buspar)
Cerivastatin (Baycol)[5, 9]
Cilostazol (Pletal)[5]
Cisapride (Propulsid, Prepulsid)[9]
Colchicine[5]
Eletriptan (Relpax)[5]
Etoposide (Vepesid)[8, 10]
Halofantrine (Halfan)
Lovastatin (Mevacor)
Mifepristone (Mifeprex)[5]
Pimozide (Orap)[5]
Quinidine (Quinaglute, Quinidex)[8, 10]
Sildenafil (Viagra)
Simvastatin (Zocor)[8]
Sirolimus (Rapamune)[1, 5]
Terfenadine (Seldane)[9]
Ziprasidone (Geodon)[5]

Table 2: Use with grapefruit with caution

Albendazole (Albenza)	**Losartan (Cozaar)**
Alfentanil (Alfenta)[8]	**Methadone (Dolophine)[5]**
Alfuzosin (Uroxatral)[5]	**Methylprednisolone (Medrol)[8]**
Almotriptan (Axert) [5]	**Midazolam (Versed)[8]**
Aprepitant (Emend)[5]	**Montelukast (Singulair)[5]**
Aripiprazole (Abilify) [5]	**Nicardipine (Cardene)[8]**
Bupropion (Wellbutrin, Zyban)[5]	**Nifedipine (Procardia)**
Carbamazepine (Tegretol)[3]	**Nimodipine (Nimotop)**
Cinacalcet (Sensipar)[5]	**Nisoldipine (Sular)**
Clomipramine (Anafranil)	**Oxybutynin (Ditropan)[5]**
Cyclosporine (Neoral)[2, 3, 8]	**Propafenone (Rythmol)[5 , 11]**
Darifenacin (Enablex)[5]	**Quetiapine Fumarate (Seroquel)[5]**
Delavirdine (Rescriptor)[5]	**Quinine**
Dextromethorphan	**Ramelteon (Rozerem)[5]**
Diazepam (Valium)[8]	**Saquinavir (Invirase)[2]**
Dofetilide (Tikosyn)[5]	**Sertraline (Zoloft)**
Efavirenz (Sustiva)[5]	**Solifenacin (Vesicare)[5]**
Erlotinib (Tarceva)[5]	**Tacrolimus (Prograf)[2, 3, 8]**
Erythromycin(Eryc,E-Mycin, Erythromid, Erybid)[8]	**Tamoxifen (Nolvadex)[5]**
Eszopiclone (Lunesta)[5]	**Tamsulosin (Flomax)[5]**
Felodipine (Renedil, Plendil)	**Tolterodine (Detrol)[5]**
Fexofenadine (Allegra)[10]	**Triazolam (Halcion)**
Fluvoxamine (Luvox)	**Trazodone (Desyrel)[5]Simvastatin (Zocor)[8]**
Gefitinib (Iressa)[5]	**Sirolimus (Rapamune)[1, 5]**
Imatinib Mesylate (Gleevec/Glivec)[5]	**Terfenadine (Seldane)[9]**
Indinavir (Crixivan)[10]	**Ziprasidone (Geodon)[5]**
Itraconazole (Sporanox)[10]	

Prevalence of drug interactions

More than 85 drugs claim to have the potential to interact with grapefruit[18]. More than half of these interactions are theoretically capable of causing serious adverse effects. Between 2008 and 2012, the number of drugs

with potentially serious adverse effects related to grapefruit juice more than doubled. Grapefruit juice is speculated to interact with several classes of commonly used drugs, including the following: CCBs, antiarrhythmic agents, 3-hydroxy-3-methylglutaryl-coenzyme (HMG-CoA) reductase inhibitors (statins), phosphodiesterase type 5 (PDE-5) inhibitors, central nervous system modulators, immunosuppressants, antiviral agents, antibiotics, and antihistamines[19,20]. Use of medications with Grape fruit has shown in Table 1,2,3 and 4[21].

Table 3: Medications with no significant interaction with grapefruit

Acebutolol (Monitan, Sectral)[4]
Alprazolam (Xanax)[4]
Amlodipine (Norvasc)[4]
Amprenavir (Agenerase)[4, 10]
Caffeine[4, 8]
Carvedilol (Coreg)[4]
Clarithromycin (Biaxin)
Clozapine (Clozaril)[4]
Digoxin (Lanoxin)[8]
Diltiazem (Cardizem)[4, 8]
Eplerenone (Inspra)[4]
Ethinyl Estradiol[4, 8]
Fentanyl (Actiq)[4, 8]
Haloperidol (Haldol)[8]
Lansoprazole (Prevacid)[4, 8]
Levothyroxine (Eltroxin, Synthroid)[4, 8]
Omeprazole (Losec, Prilosec)[4]
Phenytoin (Dilantin)[8]
Pravastatin (Pravachol)
Prednisone (Deltasone)
Scopolamine (Hyoscine)[4, 8]
17-□□ Estradiol[4, 8]
Telithromycin (Ketek)[4]
Theophylline (Theo-Dur, Uniphyl)
Verapamil (Calan, Isoptin, Verelan)[8]
Warfarin (Coumadin)[8]

Factors that may increase the risk of drug interactions with grapefruit

Thousands of drugs are available for prescription and over-the-counter use and most of the population takes at least one pharmacological agent on a regular basis[2,21]. For patients taking 2 medications, the theoretical risk of an interaction with another drug, food, or nutrient is 15%; for patients taking 5 medications, the risk of an interaction is 40%; and for patients taking 7 or more medications, an interaction is nearly certain, with a risk of 80%[17].

Table 4: Medications considered safe for use with grapefruit

Cetirizine (Zyrtec, Reactine)[6]
Desloratadine (Aerius, Clarinex)[7]
Fluvastatin (Lescol)[7]
Loratadine (Claritin)[6]
Fluvastatin (Lescol)[7]
Loratadine (Claritin)[6]

Genetic, pathophysiological, and environmental factors contribute to the differences in therapeutic response and the appearance of adverse reactions. Such variations can prevent or delay optimal outcomes and impact health care and quality of life[3].
Patients with cancer, malnourished patients, patients with gastrointestinal tract defects or dysfunction, immunocompromised patients, patients receiving enteral nutrition, liver cirrhosis and patients with chronic diseases that require multiple drugs for treatment are especially at increased risk for food-drug interactions[2,3,21].

Older adults are also at increased risk for all types of food-drug and drug-drug interactions because they are often using multiple medications and have a decreased capacity for drug absorption, distribution, metabolism, and excretion[2,6,9]. Specifically with regard to the CYP450 system, older adults have decreased hepatic enzyme activity[6]. The risk for food and drug interactions is most probable in people older than 70 years of age[15].

Many factors affect the clinical significance and relevance of grapefruit-drug interactions, including the bioavailability of the drug, the intrinsic level of CYP3A4 or drug transporters in the intestine, the amount and frequency of grapefruit consumption, as well as the species of the grapefruit ingested and its geographical origin, maturity, manufacturing process, storage conditions, and seasonal variability[5,8,9,15,25,32,34]. Drugs that have a narrow therapeutic index or a steep concentration- response relationship are also more likely to exhibit clinically significant interactions when used with grapefruit[2,10,33-35].

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