

Interactions of Grapefruit Juice with Drugs

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Interactions between grapefruit juice and oral drugs have been reported in the literature. The constituents of the juice that give rise to pharmacokinetic interactions have not been identified with certainty. It has been suggested that the mechanisms may involve inhibition of intestinal cytochrome P450 CYP3A4 isozyme and of drug efflux transporters. There are several variables that may influence the clinical significance of the drug-food interactions. In the pharmacy practice setting, the major concern is the increased bioavailability of drugs having a narrow therapeutic index.

Introduction

An interaction may occur in the body when a drug is taken concomitantly with other drugs or foods or in the presence of environmental chemical agents. The outcome of an interaction is a change in the effect that a drug exerts on the body. While this effect may at times be beneficial if it enhances the therapeutic benefit of the drug it may, at other times, prove to be harmful if toxicity ensues or if efficacy is reduced¹.

Drug-food interactions are often associated with changes in the absorption of a drug when in the presence of specific foods. A common example is the reduced intestinal absorption of tetracycline in the presence of dairy products. However other pharmacokinetic mechanisms, such as the influence of drug metabolism on the bioavailability of drugs and on the serum level of active drug substances, should not be excluded.

An important drug-food interaction that is receiving increasing attention occurs between grapefruit juice and drugs belonging to several therapeutic categories. The common factor that links these interactions with grapefruit juice appears to be a drug metabolising enzyme that plays a fundamental role in the detoxification of many drugs.

Cytochrome P450 metabolising enzymes

The metabolic routes by which drugs are biotransformed in the body are divided into two phases. Phase I reactions prepare a drug for the subsequent Phase II reactions that are the true detoxification pathways which result in products that are generally water-soluble and easily excreted².

The mixed-function oxidase (MFO) reaction catalysed by cytochrome P450 dominates Phase I metabolism.

Hundreds of structurally diverse drugs and chemicals are substrates for the MFO system found in microsomes (endoplasmic reticulum) of cells primarily of the liver, kidney, lung and intestine².

The enzyme, cytochrome P450 (CYP), is a haemoprotein and consists of a family of closely related isozymes embedded in the membrane of the endoplasmic reticulum². Of the many isozymes isolated from human liver tissue, only a few subfamilies are responsible for about 90% of the metabolism of commonly used drugs. The predominant isozymes are designated as CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4¹. The CYP3A subfamily is the most abundant in human liver microsomes. Of these,

the isozyme CYP3A4 appears to be found in all human livers and is also expressed in extrahepatic tissues such as the small intestine³. Table I lists examples of drugs that are substrates for CYP3A4.

Grapefruit juice and CYP3A4

The interactions between grapefruit juice and drugs are believed to be the result of inhibition of CYP3A4 by substances present in the juice¹. Since the isozyme is located both in the intestinal wall and in the liver, the drug-food interaction could influence absorption of an oral dose of a drug and its hepatic first-pass metabolism. The resultant effect of enzyme inhibition is manifested as an increase in plasma drug levels due to an

increase in absolute bioavailability⁴.

The drug-food interaction involving grapefruit juice is not known to occur when the fruit is eaten as opposed to drinking its juice⁵. Neither have similar interactions been seen with orange juice⁴. It appears that flavonoids found in grapefruit juice but not in orange juice may inhibit the CYP3A4 isozyme.

The major flavonoid found in grapefruit juice, the glycoside naringin, does not appear to affect human cytochrome P450 enzymes. However, naringin may be hydrolysed in the intestine to naringenin, a potent inhibitor of enzymes such as CYP3A4 and CYP1A2⁴. In fact, the increase in bioavailability of several calcium channel blockers, ethinyloestradiol, oral cyclosporin and benzodiazepines when taken with grapefruit juice may be due to inhibition of the CYP3A4 isozyme by naringenin¹.

The furanocoumarin^{6,7} Dihydroxybergamottin is another inhibitor of CYP3A4 that is found in grapefruit juice^{6,7}. It has been shown to be the major furanocoumarin responsible for a decrease in CYP3A4 activity and a reduction in cellular concentrations of the enzyme as a result of accelerated degradation⁶.

Inhibition of CYP3A4 does not appear to be the only mechanism that accounts for the drug-food interactions. Constituents of grapefruit juice that are different from CYP3A4 inhibitors are known to enhance drug absorption by inhibiting intestinal drug efflux transporters such as P-glycoprotein⁸. This is an ATP-dependent membrane transporter known as multidrug resistance protein³ which extrudes drug molecules from epithelial cells of the villi into the intestinal lumen thus reversing the process of absorption.

Table I
Examples of drugs metabolised by cytochrome P450 CYP3A4 isozyme
(adapted from Klaassen, 1996 and Stockley, 1999)

Pharmacological/ Therapeutic Class	Drug Metabolised by CYP3A4
Analgesics	Alfentanil • Paracetamol
Anti-arrhythmics	Amiodarone • Lidocaine • Propafenone • Quinidine
Antibacterials	Clindamycin • Dapsone • Erythromycin • Troleandomycin
Antidepressants	Amitriptyline • Clomipramine • Imipramine • Nefazodone • Sertraline • Venlafaxine
Antiepileptics	Carbamazepine • Clonazepam • Zonisamide
Antihistamines	Astemizole • Loratadine • Terfenadine
Antihypertensives	Losartan
Antivirals	Indinavir • Nelfinavir • Nevirapine • Ritonavir • Saquinavir
Anxiolytics and/or Hypnotics	Alprazolam • Diazepam • Midazolam • Triazolam • Zolpidem
Bronchodilators	Theophylline
Calcium-channel blockers	Diltiazem • Felodipine • Nifedipine • Nimodipine • Nisoldipine • Verapamil
Cardiac glycosides	Digitoxin
Corticosteroids	Budesonide • Dexamethasone • Hydrocortisone
Cough suppressants	Dextromethorphan
Cytotoxic drugs	Cyclophosphamide • Etoposide • Ifosfamide • Paclitaxel • Teniposide
Gastric motility stimulants	Cisapride
Hormone antagonists	Flutamide • Tamoxifen • Toremifene
Immunosuppressants	Cyclosporin • Tacrolimus (FK-506)
Lipid-regulating drugs	Lovastatin • Simvastatin
Oral anticoagulants	Warfarin
Proton pump inhibitors	Lansoprazole • Omeprazole
Sex hormones	Ethinylloestradiol • Testosterone

Table II
Examples of the outcome of studies on the effects of grapefruit juice on drugs (Adapted from Stockley, 1999)

Drug	Effect of Grapefruit Juice	Outcome
Acenocoumarol (nicoumalone)	<ul style="list-style-type: none"> No significant effect detected 	<ul style="list-style-type: none"> No clinically relevant interaction Grapefruit juice need not be avoided
Astemizole	<ul style="list-style-type: none"> No effect detected 	<ul style="list-style-type: none"> No clinically relevant interaction Grapefruit juice need not be avoided
Benzodiazepines	<ul style="list-style-type: none"> Increased bioavailability of midazolam, triazolam and diazepam probably due to inhibition of metabolism by CYP3A4 	<ul style="list-style-type: none"> Interactions of minor importance
Calcium channel blockers	<ul style="list-style-type: none"> Increased bioavailability of felodipine with increase in drug effects and in side effects Increased bioavailability of amlodipine, nicardipine, nifedipine, nimodipine, nisoldipine and nitrendipine without adverse haemodynamic effects Increase in bioavailability likely to be due to inhibition of metabolism by CYP3A4 Bioavailability of diltiazem is unaltered 	<ul style="list-style-type: none"> Grapefruit juice to be avoided with calcium channel blockers (other than amlodipine and diltiazem)⁵
Cilostazol	<ul style="list-style-type: none"> Increase in drug activity is likely due to metabolism by CYP3A4 	<ul style="list-style-type: none"> No serious interaction is likely to occur Recommended that grapefruit juice be avoided
Cyclosporin (Ciclosporin)	<ul style="list-style-type: none"> Increase in bioavailability probably due to inhibition of metabolism by CYP3A4 	<ul style="list-style-type: none"> Interaction is clinically important Grapefruit juice to be avoided unless serum cyclosporin levels are monitored
Ethinylestradiol (Ethinylestradiol)	<ul style="list-style-type: none"> Increased bioavailability possibly due to inhibition of metabolism 	<ul style="list-style-type: none"> No clinically relevant interaction Grapefruit juice to be avoided
Indinavir	<ul style="list-style-type: none"> Reduced bioavailability 	<ul style="list-style-type: none"> No clinically relevant interaction Grapefruit juice to be avoided
Lovastatin	<ul style="list-style-type: none"> Increased bioavailability likely due to inhibition of metabolism by CYP3A4 	<ul style="list-style-type: none"> Interaction is clinically significant Grapefruit juice to be avoided
Prednisone and Prednisolone	<ul style="list-style-type: none"> No significant effect detected 	<ul style="list-style-type: none"> No clinically relevant interaction Grapefruit juice need not be avoided
Quinidine	<ul style="list-style-type: none"> Delayed absorption Inhibition of metabolism by CYP3A4 	<ul style="list-style-type: none"> No clinically relevant interaction Grapefruit juice need not be avoided
Saquinavir	<ul style="list-style-type: none"> Increased drug bioavailability and serum drug level 	<ul style="list-style-type: none"> No clinically relevant interaction Drug dose adjustment not required in the presence of grapefruit juice
Tacrolimus (FK-506)	<ul style="list-style-type: none"> Increased serum drug level probably due to inhibition of metabolism 	<ul style="list-style-type: none"> Interaction is clinically significant Grapefruit juice to be avoided unless serum tacrolimus levels are monitored
Terfenadine	<ul style="list-style-type: none"> Increased serum drug levels leading to drug accumulation in the body and potentially life-threatening cardiotoxicity Metabolism by CYP3A4 of the parent drug to the active metabolite is inhibited 	<ul style="list-style-type: none"> Interaction is clinically important Grapefruit juice to be avoided
Theophylline	<ul style="list-style-type: none"> No interaction detected 	<ul style="list-style-type: none"> No clinically relevant interaction Grapefruit juice need not be avoided

Clinical relevance of the interactions

Altered pharmacokinetic parameters are observed when an oral drug interacts with grapefruit juice. The increase in drug bioavailability is attributed to an increase in the maximal plasma concentration (C_{max}), the time to reach maximal concentration (t_{max}) and the area under the plasma concentration-time curve (AUC). No changes have been observed in total body clearance (Cl), elimination half-life ($t_{1/2}$) and volume of distribution (V_D)⁴.

Studies conducted under controlled conditions and using standardised grapefruit juice can only give an indication of the significance of the drug-food interactions. In clinical practice the situation may be rather different due to several variables that can be identified^{1,4,9,10}.

These include:

- the amount of juice co-administered with the drug;
- the concentration of the juice preparation (regular versus double strength);
- the brand of juice and the proportion of specific constituents (differences exist between commercially available preparations and between preparations and freshly squeezed juice);
- the time/duration of administration of the juice (interactions do not occur solely with concurrent administration of the drug and juice; a decrease in intestinal CYP3A4 has been shown to occur within 4 hours of ingestion of a single glass of juice⁶; the duration of inhibition can last 24 hours and repeated juice consumption may result in a cumulative drug increase in the body¹⁰; it is unclear how long the interval between drinking the

juice and taking the drug should be in order to limit the possibility of an interaction⁵);

- the regularity of juice intake during a course of drug treatment (occasional ingestion of juice as opposed to regular intake could lead to fluctuations in the plasma drug concentration with altered drug effects/toxicity);
- the variability in first-pass metabolism in the population;
- the extent to which a given drug is susceptible to first-pass metabolism;
- the extent of variability in intestinal CYP3A4 activity in the population (due to differences in CYP3A4 protein expression);
- the extent to which a drug is metabolised at the intestinal wall;
- the variability in bioavailability in the population for any given drug (this may be greater than the increase in bioavailability seen as an interaction with grapefruit juice); and
- the variability in serum drug levels in the population for any given drug.

Although there are many drugs that are metabolised by CYP3A4 (Table I) the clinical significance of an interaction with grapefruit juice depends on the beneficial or detrimental effect that this may have on the individual and on the extent of that effect. The examples shown in Table II demonstrate that, while there may be evidence of an interaction, the resultant effect may not be of significance and therefore is not of concern for the safety of the patient. The major concern arises with drugs having a relatively narrow therapeutic

window, since an increase in drug toxicity at a given dose is more probable given the higher bioavailability⁹. In decreased hepatic or renal function, where drug clearance and elimination are reduced, an increase in drug effect or in toxicity may become more evident depending on the pharmacokinetics and the therapeutic index of the drug.

Drug-grapefruit juice interactions could be of benefit when a drug has low oral bioavailability. The beneficial effect is seen when bioavailability and plasma concentration increase without the need for an increase in the dose, the dosing frequency or the cost of drug therapy⁴. Cyclosporin has low oral bioavailability because of significant intestinal metabolism. The drug is not rapidly metabolised by CYP3A4 but has a long absorption phase (lasting up to 8 hours in some patients) that increases exposure of the drug to the enzyme¹¹. Enzyme inhibition results in an increase in bioavailability of cyclosporin that may lead to increased nephrotoxicity. However, in cyclosporin therapy, CYP3A4 inhibitors such as diltiazem or ketoconazole are administered concurrently with the immunosuppressant in order to raise the bioavailability of cyclosporin so that the dose of the drug can be reduced while still achieving therapeutic plasma concentrations. In real terms, this proves to be advantageous because of the lower cost of therapy. It has been suggested that grapefruit juice could be used to achieve this effect because it is inexpensive, nutritious and lacks the systemic effects of diltiazem or ketoconazole¹. However the variables discussed above would preclude this approach. Furthermore, the variability in enzyme inhibition may lead to an increase in the cost of laboratory monitoring of plasma drug concentrations that could offset the decrease in the cost of cyclosporin therapy⁴.

Conclusion

The importance of drug-grapefruit juice interactions should be judged on the basis of the therapeutic index, pharmacokinetics and the increased effect or toxicity of the drug and the variables that influence the interactions. Where the negative effects of an interaction have been shown to occur with a substantial exposure to grapefruit juice that is not likely to be encountered in normal diets, the clinical significance of a potential interaction becomes limited⁹. In the pharmacy practice setting, the dietary habits of the patient should be taken into account when dispensing drugs that may potentially interact with foods. In the case of interactions with grapefruit juice, more attention should be afforded to drugs having a narrow therapeutic index that may potentially interact with the food. ★

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Websites of Interest

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Journals

With the expansion of the Internet, an ever-increasing number of medical and pharmaceutical journals are making their contents available on-line. The level of free access to these journals varies widely: some are limited to tables of contents, others to article abstracts and the occasional journal allows full-text access. The following are some leading journals that allow at least access to the abstracts of articles.

Annals of Allergy, Asthma, & Immunology http://allergy.edoc.com/	Journal of the American Medical Association http://jama.ama-assn.org/
British Medical Journal (BMJ) http://www.bmj.org	Medical Care http://www.medicalcare.org/
Diabetes Care http://care.diabetesjournals.org/	Morbidity and Mortality Weekly Report http://www.cdc.gov/mmwr/
Free Medical Journals http://www.freemedicaljournals.com	New England Journal of Medicine http://www.nejm.org
Hypertension http://hyper.ahajournals.org	The Lancet http://www.thelancet.com/journal

Miscellaneous

A number of other web sites provide useful information with links to latest updates and even more journals. The following sites offer updated drug information.

Drug Infonet http://www.druginfonet.com	Pharmweb http://www.pharmweb.net
Drug Information Association http://www.diahome.org	Rx List http://www.rxlist.com
E-medicine.Com http://www.emedicine.com	Health Gate http://www.healthgate.com
Helix http://www.helix.com	Medscape http://www.medscape.com
Mayo Clinic http://www.mayohealth.org	The Synapse http://www.thesynapse.net