INTERACTION BETWEEN GRAPEFRUIT JUICE AND DRUGS*

Junichi AZUMA**


Abstract: There is a possibility that even a glass of grapefruit juice (GFJ) taken several hours before oral medication may enhance the bioavailability of many drugs, exaggerate the drug action, and increase the toxic effect by exaggerating the potency of the drug. This can be explained by inhibition of CYP3A4 in the small intestine by GFJ, thus suppressing drug metabolism. This interaction with GFJ is likely to occur mainly with those drugs that are metabolized by CYP3A4 and are associated with low bioavailability when given via an oral route. Thorough instruction on medication is necessary when these drugs are administered to patients. Examples of these drugs include: dihydropyridine calcium antagonists, terfenadine, cyclosporine, and carbamazepine.

Key words: Grapefruit juice; Cytochrome P450 (CYP); CYP3A4; Drug interactions; Enzyme inhibition

Introduction

Even a glass of grapefruit juice taken several hours before medication may increase the bioavailability of many drugs, raise the blood concentration of the drug, enhance drug potency, or exaggerate the toxic action of a certain drug. This occurs because of the inhibition of metabolic activity of CYP3A4, a molecular species of drug metabolizing enzyme, P450, that exists in the small intestine.

A drug that has been administered via an oral route is absorbed through the digestive tract, reaches the liver via the portal system, appears in the peripheral circulation, and is then distributed throughout the body. Part or most of a drug is subjected to a first-pass metabolism in the liver and small intestine. Many drugs are highly oil-soluble and they have to be metabolized by a metabolic enzyme called cytochrome P450 into water-soluble compounds that can be excreted in the urine or bile. The most important drug-metabolizing enzymes in the human are the following 5: CYP1A2, CYP2C9, CYP2C91, CYP2D6, and CYP3A4. Among the P450 enzymes that exist in the human liver, the amount of CYP3A4 is the greatest (about 30%). CYP3A4 also exists in the small intestine and is the most important enzyme, participating in more than one-half of the pharmaceutical agents.

* This article is a revised English version of a paper originally published in the Journal of the Japan Medical Association (Vol. 123 No. 7, 2000, pages 1013-1016). The Japanese text is a transcript of a lecture originally aired on November 26, 1999, by the Nihon Shortwave Broadcasting Co., Ltd., in its regular program “Special Course in Medicine”.

** Professor, Postgraduate School of Pharmaceutical Science, Osaka University
Drug Interactions: Grapefruit Juice

The development of adverse effects of drugs caused by “drug interactions”, which has attracted attention recently, occurs when 2 or more drugs are taken simultaneously or almost at the same time. A typical example is an adverse effect of sorivudine, which is caused when the process in which 5 FU, an antineoplastic agent, is metabolized and inactivated is inhibited by the metabolites of sorivudine. If a drug-metabolizing enzyme is inhibited, the blood concentration of the active unchanged drug increases, thus amplifying the pharmacological action or causing adverse effects to develop.

An abnormal rise in the blood concentration of a drug is called an interaction by “inhibition” of a drug-metabolizing enzyme. The blood concentration of a drug that has been affected by inhibition rises but a clinical problem arises only with drugs (such as fluorouracil) that have a narrow safety range for their blood concentration and may readily develop serious adverse effects.

Recently, the drug interaction of grapefruit juice has been frequently reported. An interesting action of this juice in increasing the bioavailability of an orally taken drug was accidentally discovered about 10 years ago when it was given to cover the taste of ethanol during a study of the interaction between felodipine (a dihydropyridine type Ca blocker) and ethanol.1) Later, it was shown that grapefruit juice raises the mean area under the felodipine plasma concentration-time curve (AUC) approximately 3-fold when the felodipine was administered orally to patients with borderline hypertension. It was reported that grapefruit juice exaggerated the antihypertensive effects of felodipine, raised the heart rate in clinical patients, and was frequently responsible for adverse effects due to vasodilation.2) Grapefruit juice significantly raised the maximum plasma concentration (Cmax) of felodipine but did not change its half-life (t1/2). Because this juice had no effect on the pharmacokinetics of felodipine when administered via an intravenous route, it was concluded that the action of grapefruit juice stems from its metabolic inhibition in the stage before the drug enters the circulating blood.

Mechanism Responsible for Interactions Caused by Grapefruit Juice

To discover the action of grapefruit juice on the drug-metabolizing enzymes of the small intestine and liver in man, a clinical study that is not possible in Japan was conducted.3) Consequently, it became evident that this juice selectively participated in post-translational regulation of CYP3A4 in the small intestine, reduced the CYP3A4 content by about 50%, and compromised the metabolic activity of the enzyme. Specifically, drinking grapefruit juice for 5 consecutive days caused a 3-fold increase in the AUC of felodipine and a 5-fold increase in Cmax. In this instance, there were no changes in the CYP3A4 mRNA level of the small intestine; but the protein contents of CYP3A4 and CYP3A5 were reduced by a mean of 62%. No changes were noted in the activity of the hepatic CYP3A4—detected by a method called an erythromycin breath-test—or the protein contents for CYP2D6 or CYP1A1 in the small intestine. Thus it was concluded that grapefruit
juice selectively inhibits a molecular species of CYP3A in the small intestine and raises the bioavailability of felodipine.

Orange juice is not associated with the inhibitory actions described above. Because the expression of a molecular species of CYP3A is reduced by grapefruit juice, it is evident that this inhibition is not a simple competitive action on the metabolism of the substrate. Grapefruit juice reduced the post-translational CYP3A4 protein content without affecting CYP3A4 mRNA in the small intestine, suggesting that this is an irreversible enzyme inhibition with probable enhancement of CYP3A4 decomposition. To restore the CYP3A4 activity, de novo synthesis of the enzyme becomes necessary.

The potency of the inhibitory action of grapefruit juice varies in individuals: Some are not much affected while in others the AUC and Cmax of the plasma felodipine rose to 6 times that when water was given instead of the juice. Because the expression of CYP3A4 protein in the small intestine is involved in the reaction and the inhibitory rate is exaggerated in individuals with greater CYP3A4 activity, it is suspected that this individual difference in the potency of the interaction caused by the grapefruit juice is at least partly due to some genetic difference. The details have yet to be elucidated.

It is presumed that in this phenomenon, a “certain component” in the grapefruit juice participates in the inhibition of CYP3A4 activity. It is understood that this “certain component”, when taken orally, is trapped in the small intestine without reaching the liver and inhibits the CYP3A4 activity that is expressed by the villous cells of the small intestine. Initially, it was believed that flavonoids, such as naringen and naringenin, and 6',7'-dihydroxybergamottin of the furanocoumarin type that are contained in grapefruit juice, were strongly suspected to be causative agents for inhibition. However, recent reports negated the possibility that these act as major causative agents in the interactions between grapefruit juice and a drug.

Recently, a component that potently inhibits CYP3A4 was discovered in an ethylacetate extract of grapefruit juice. Structural analysis revealed that this was a new furanocoumarin derivative. However, clinical studies will be needed to prove its clinical significance in drug interactions.

**Drugs That Are Affected by Grapefruit Juice**

The drugs that may interact with grapefruit juice are those that are metabolized by CYP3A4. The most frequently investigated are dihydropyridine-type Ca blockers; their metabolic pathways are similar but the bioavailability of each drug varies widely. Nisoldipine has the lowest bioavailability and is most likely to be affected by grapefruit juice, followed by felodipine, nicardipine, and nitrendipine, while the effect on nifedipine and amlodipine are negligible.

It is known that the magnitude of the effect of grapefruit juice is proportional to the first-pass effect (the greater the first-pass effect, the lower the bioavailability). It is difficult to determine an individual’s drug interaction for the dihydropyridine-type drugs with low bioavailabilities. Individual difference is at the greatest for nisoldipine. Among nifedipine-type drugs, the effect of grapefruit
juice is slightly more pronounced for enteric-coated preparations.

In addition to these dihydropyridine-type drugs, it has been confirmed that more than 20 drugs interact with grapefruit juice, resulting in clinical problems. Even at this time, the results of a number of clinical studies attest to these effects. Among the drugs that are marketed in Japan and metabolized by CYP3A4, those that have known clinical problems due to their interactions with grapefruit juice are: Terfenadine, saquinavir, cyclosporine, midazolam, triazolam, and verapamil (Table). The plasma concentrations of those drugs that are raised significantly when combined with itraconazole or erythromycin, known inhibitors of hepatic CYP3A4 activity, are also affected by grapefruit juice. Cisapride and astemizole are also affected by grapefruit juice. It is believed that those drugs that are not very likely to be affected with the combination of CYP3A4 inhibiting drugs are also relatively untouched by the actions of grapefruit juice.

There are several recent reports on the different effect of grapefruit juice between water-soluble HMG-CoA reductases and oil-soluble preparations that constitute metabolic substrates for CYP3A4. It is reported that grapefruit juice does not affect the pharmacokinetics of water-soluble preparations, while drinking of the juice together with oil-soluble preparations that are metabolized mainly by CYP3A4 results in significant increases in the plasma concentrations of these preparations (AUC, 1.4 to 15 times that when taken with water, though varying in degree for each drug).

**Notes on Therapy**

When a drug that may undergo an interaction with grapefruit juice is to be prescribed, it is necessary to give appropriate instructions to patients at medication. The following clinical notes are suggested.

The duration of the inhibitory action by grapefruit juice is an important clinical topic. The correlation between the consumption of grapefruit juice and

<table>
<thead>
<tr>
<th>Drugs That Are Affected by Grapefruit Juice</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Dihydropyridine-type Ca blockers:</td>
</tr>
<tr>
<td>nisoldipine, felodipine, nicardipine, nifedipine, etc.</td>
</tr>
<tr>
<td>- Drugs acting on the central nervous system:</td>
</tr>
<tr>
<td>benzodiazepam-type hypnotic sedatives (triazolam and midazolam), carbamazepine, and diazepam</td>
</tr>
<tr>
<td>- HMG CoA reductase inhibitors:</td>
</tr>
<tr>
<td>lovastatin, simvastatin, etc.</td>
</tr>
<tr>
<td>- Immunosuppressive agents:</td>
</tr>
<tr>
<td>cyclosporine and tacrolimus.</td>
</tr>
<tr>
<td>- Anti-allergy agents:</td>
</tr>
<tr>
<td>terfenadine and astemizole</td>
</tr>
<tr>
<td>- HIV protease inhibitors:</td>
</tr>
<tr>
<td>saquinavir</td>
</tr>
<tr>
<td>- Others:</td>
</tr>
<tr>
<td>cisapride and verapamil</td>
</tr>
</tbody>
</table>
felodipine administration has been studied.\textsuperscript{7)} When a glass (220 ml) of grapefruit juice is consumed 4 hours before or at the time of drug administration, the rates of increases of AUC and Cmax became the greatest. The potency of the interaction attenuated as the interval between grapefruit juice ingestion and felodipine administration increased; but the Cmax of felodipine was still obviously high even when the drug was administered 24 hours after grapefruit juice ingestion.

We conducted a study on the effect of grapefruit juice on nisoldipine pharmacokinetics in 8 healthy Japanese subjects.\textsuperscript{8)} When nisoldipine was administered together with 250 ml of grapefruit juice, the Cmax and AUC of the plasma concentration of the drug increased 3 and 4.5 times, respectively, in comparison with the corresponding amounts when water was used instead of grapefruit juice. If the juice was given, followed by the drug together with water one hour later, Cmax and AUC increased about 4- and 5-fold, respectively. However, no notable changes in pharmacodynamics were noted when grapefruit juice was ingested one hour after medication.

The half-life of the inhibitory effect of grapefruit juice has been generally estimated to be 12 hours. Imbibing this juice on a single occasion may result in a sustained effect for more than 24 hours, which calls for special clinical attention.

What is important next is the extent of changes in the dynamics of the blood contents of the affected drugs. The following types of drugs are considered to pose a clinical risk when combined with grapefruit juice: (1) Those for which the pharmacological actions may be potentiated, causing excessive reactions or toxic responses when their plasma concentrations exceed twice the desired level: examples include some dihydroxypyridine-type Ca blockers, terfenadine, and saquinavir; (2) those drugs that are associated with sharply curved concentration (dosage)-response relationship; and (3) those with narrow therapeutic ranges and possible potentiation of the drug effects, resulting in excessive drug actions or toxic reactions; these should be watched carefully in clinically practice even when their plasma concentrations may not be excessively high; examples include cyclosporine, midazolam, triazolam, and verapamil.

Finally, the following patient factors are cited in relation to drug interactions with grapefruit juice: (1) A centuated CY P3A 4 activity of the small intestine; and (2) hepatic insufficiency.

The type and quantity of grapefruit juice consumed are also important. Interactions between commercially available grapefruit juice (frozen and concentrated, condensed or diluted, and fresh frozen) and felodipine have been proven; but their magnitude depends on the amount of the active components and may vary, even within each brand or lot. Many of the studies have used grapefruit juice that was condensed twice but it would be safe to assume that all grapefruit juice has the potential to act in the way that has been described here.

Even a single glass of grapefruit juice imbibed several hours earlier may augment the bioavailability, cause excessive drug effects, or exaggerate the toxic actions of the drugs that have been cited above. Particular attention should be paid to these matters in clinical practice.
REFERENCES