REVIEW

Food–drug interaction: grapefruit juice augments drug bioavailability—mechanism, extent and relevance

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More than a decade has passed since it was unintentionally discovered that grapefruit juice interacts with certain drugs. The coadministration of these drugs with grapefruit juice can markedly elevate drug bioavailability, and can alter pharmacokinetic and pharmacodynamic parameters of the drug. The predominant mechanism for this interaction is the inhibition of cytochrome P-450 3A4 in the small intestine, resulting in a significant reduction of drug presystemic 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. Some calcium channel antagonists, benzodiazepines, HMG-CoA reductase inhibitors and cyclosporine are the most affected drugs. A single exposure to one glass of the juice can usually produce the maximal magnitude of the interaction. The data available so far, concerning this interaction and its clinical implications, are reviewed in this article. It is likely that more information regarding this interaction will accumulate in the future, and awareness of such is necessary for achieving optimal drug therapy.

Keywords: grapefruit; drug interaction; pharmacokinetics; bioavailability; cytochrome P-450 3A4; P-glycoprotein

Introduction

Frequently, during drug therapy, a patient is treated with more than one medicine concurrently in order to treat one or more medical problem. By most accounts, the available information concerning drug influences is valid for each drug separately, while concomitant intake of two or more drugs can alter their influences. Hence, an interaction is said to take place when the effects of one drug are changed by the presence of another drug, food, drink or by some environmental chemical agent.

An investigation was designed 13 y ago to evaluate a possible interaction between ethanol intake and the dihydropyridine calcium channel blocker felodipine. Grapefruit juice was used as a flavor supplement in order to mask the alcohol taste. The concomitant intake of nonintoxicating amounts of ethanol and felodipine resulted in several fold higher felodipine concentrations than observed in other investigations of felodipine pharmacokinetics. In addition, lower blood pressure and higher frequencies of adverse effects were measured compared with felodipine alone (Bailey et al., 1989). An examination for possible causes failed to explain this surprising observation, until, eventually, a pilot research in a single volunteer was conducted to assess the role of the juice (Bailey et al., 1998). Further follow-up studies confirmed that grapefruit juice elevated dramatically felodipine bioavailability and could alter pharmacokinetic and pharmacodynamic parameters of the drug (Bailey et al., 1991). This incidental discovery has led to the publication of numerous articles regarding the interaction between grapefruit juice and various drugs, focusing on different aspects: interaction mechanisms, grapefruit juice constituents that are responsible for the interaction, drugs exhibiting the interaction and the clinical relevance.

Mechanisms

Cytochrome P-450 (CYP450) is a large family of enzymatic proteins that catalyze the oxidation of substrate molecules.
Many endogenous compounds, as well as a large number of foreign compounds, including drugs, are metabolized in the body by CYP450 through this oxidative biotransformation. The isoenzyme cytochrome P-450 3A4 (CYP3A4) is the predominant CYP form in the human small intestine (Kolars et al., 1992), while only a very limited number of other CYP isoforms are expressed in this organ (Zhang et al., 1999). The main mechanism for enhanced bioavailability of drugs by grapefruit juice is, presumably, the inhibition of CYP3A4 in the small intestine (Edwards et al., 1996; Lown et al., 1997), resulting in a significant reduction of drug presystemic metabolism. This inhibition was reported in an in vivo investigation in humans (Schmiedlin Ren et al., 1997). A decrease of 47% in enterocyte CYP3A4 concentration has been observed 4 h after drinking one glass of grapefruit juice (Figure 1). Grapefruit juice caused a significant increase in the bioavailability of drugs exhibiting the interaction, after oral dosing. However, after intravenous administration of the same drugs—grapefruit juice altered neither pharmacokinetic nor pharmacodynamic parameters (Ducharme et al., 1995; Lundahl et al., 1997; Uno et al., 2000). Hence, it has been concluded that only intestinal CYP3A4 is inhibited by grapefruit juice, while liver resident CYP3A4 enzymes are not affected. This conclusion is further supported by the finding that the interaction with grapefruit juice markedly elevated the area under the plasma concentration–time curve (AUC), while no significant change has been observed in elimination half-life or systemic clearance (Bailey et al., 1991). Owing to a lack in decrease of CYP3A4 mRNA following grapefruit juice intake (Lown et al., 1997), it appears that the mechanism for CYP3A4 inhibition by grapefruit juice is post transcriptional, possibly through facilitated degradation of the enzyme (Bailey et al., 1998).

Multiple drug resistance (MDR) transporters play a major role in the disposition of many drugs. The most extensively studied MDR transporter is the P-glycoprotein (P-gp) that reduces the fraction of drug absorbed by carrying the drug from the enterocyte back to the intestinal lumen (Gottesman et al., 1996). Grapefruit juice modifies the P-gp transporter activity. Although few data suggested an activation of P-gp efflux by grapefruit juice (Phang et al., 1993; Soldner et al., 1999), most investigators observed an inhibition of the transporter activity (Takanaga et al., 1998; Eagling et al., 1999; Wang et al., 2001; Tian et al., 2002). Recently, the β-blocker talinolol, which is a non-CYP450 substrate, yet a P-gp substrate, showed an increase in bioavailability when concomitantly taken with grapefruit juice in both in vitro and in vivo models (Spahn Langguth & Langguth, 2001).

CYP450 and P-gp share both overlapping tissue distribution and substrate specificity, thus, the differentiation between the two mechanisms is not definite. Yet, the effects of grapefruit juice–drug coadministration are most likely the result of interaction with CYP3A4, and only to a minor extent with the P-gp function.

**Constituents**

A number of constituents have been proposed to be involved in the interaction between grapefruit juice and drugs, although much of the data are controversial and at this stage it is hard to draw definite conclusions. The flavonoid naringin has been suggested as being a major component in grapefruit and is not found in other fruit juices (Kuhnau, 1976; Bailey et al., 1993a). In addition, in studies that were performed on liver microsomes, naringenin, naringin’s aglycon metabolite, showed the ability to inhibit dihydropyridine metabolism in vitro (Miniscalco et al., 1992). However, in vivo studies using isolated naringin have not shown reduced metabolism of CYP3A4 substrates (Bailey et al., 1993b). Also, grapefruit juice itself shows inhibition in vitro under conditions that do not allow the formation of naringenin (Edwards & Bernier, 1996). Thus, naringin and naringenin do not appear to be the sole contributors to the effect. Other flavonoids (quercetin, kaempferol) have also been investigated and found to show inhibitory effects in vitro (Miniscalco et al., 1992) but lack any effect in vivo (Rashid et al., 1993).

Another group of compounds that has been detected in grapefruit juice is the furanocoumarins (psoralens) that are known to be mechanism-based inactivators of CYP450, as well as being its substrates (Letteron et al., 1986), and recently have also been shown to inhibit P-gp (Wang et al., 2001). The major furanocoumarin present in grapefruit is bergamottin, which demonstrates a time- and concentration-dependent inactivation of CYP enzymes in vitro (He et al., 1998), as well as...
as its metabolite 6',7'-dihydroxybergamottin (DHB) (Edwards et al, 1996) and a number of other furanocoumarin derivatives (Ohnishi et al, 2000; Mohri & Uesawa, 2001). DHB, along with four newly isolated furanocoumarins have reproduced roughly the inhibitory potency of grapefruit juice when mixed together, while the omission of any of the components resulted in decreased potency, suggesting that all major furanocoumarins contribute to the properties of grapefruit juice (Guo et al, 2000).

It is likely that no single component is responsible for the interaction in vivo, but probably a combination of the effects of many constituents. Their complete identities and relative contributions are to be further investigated.

Amounts and timing
Some of the investigations have been conducted using regular strength grapefruit juice, while others employed double-strength juice, meaning, juice that has been reconstituted using half of the recommended amount of water. Another difference in the method of the various studies is the ingestion of a single glass vs repeated ingestions. Despite results that demonstrated higher intensity after repeated ingestions (Lilja et al, 2000a), it appears that in most cases, ingestion of a single glass (250 ml) of regular strength grapefruit juice is enough to produce the maximum effect (Rau et al, 1997; Kane & Lipsky, 2000). In this fashion, no further changes in the pharmacokinetics of felodipine have been detected following 14 days of daily intake of grapefruit juice, compared to the effects after the first glass (Lundahl et al, 1998).

Grapefruit juice does not need to be taken simultaneously with the medication, in order to produce the interaction. The bioavailability of lovastatin has been reported to be doubled, even when taken 12 h after the juice intake (Rogers et al, 1999), and the effects of grapefruit juice on felodipine have been shown to exist at about 30% of its maximum even when the drug was taken 24 h after the juice intake (Lundahl et al, 1995). The prolongation of the interaction is consistent with the pharmacological mechanism of the interaction, since biosynthesis of a new enzyme is necessary. Up to 3 days persistence of the juice impact is reported (Takanaga et al, 2000); however, it appears that an interval of 24 h between ingestion of grapefruit juice and a drug can usually prevent a potential clinically relevant interaction (Lilja et al, 2000b).

Drugs exhibiting the interaction (Table 1)
Calcium channel antagonists
The calcium channel antagonists are a family of agents that are used in the management of hypertension and angina pectoris. Numerous studies were performed in order to investigate the interaction between grapefruit juice and these agents since the interaction was first discovered with the dihydropyridine felodipine. These studies showed increases of up to 300% in AUC and up to 430% in $C_{\text{max}}$ of felodipine (Bailey et al, 1991; Edgar et al, 1992; Lown et al, 1997; Dresser et al, 2000), as well as increase in the serum concentrations of the metabolite—dehydrofeloledipine (Bailey et al, 1995; Lundahl et al, 1998). It should be noted that an especially pronounced pharmacokinetic effect has been detected among elderly subjects (Dresser et al, 2000). Most of these studies reported further decreases in diastolic blood pressure when felodipine was taken with grapefruit juice, as well as increased in haemodynamic-related adverse effects such as increased heart rate and orthostatic hypotension (Bailey et al, 1991; Lundahl et al, 1997, 1998). Other dihydropyridines exhibiting the interaction to a similar extent are nisoldipine (Bailey et al, 1993b; Takanaga et al, 2000) and nicardipine (Uno et al, 2000). A milder but significant interaction has been detected with nitrrendipine, prandipine and nimodipine that exhibited bioavailability increments of 100, 73 and 50%, respectively (Soons et al, 1991; Fuhr et al, 1998; Hashimoto et al, 1998). However, little or no effect has been detected for nifedipine and amlodipine (Rashid et al, 1993; Josefsson et al, 1996; Vincent et al, 2000). These two dihydropyridines are characterized by a high bioavailability compared to felodipine, nisoldipine and nicardipine, which can explain the lack of the interaction.

Verapamil and diltiazem are nondihydropyridines calcium channel antagonists, also extensively metabolized by CYP3A4. A significant increase in the bioavailability of verapamil has been detected in recent studies (Ho et al, 2000; Fuhr et al, 2002), in contrast to an earlier investigation which observed no effect (Zaidenstein et al, 1998). Diltiazem has been found to produce no interaction with grapefruit juice in a single study (Sigusch et al, 1994), and further investigations are needed.

The calcium channel antagonists exhibiting the interaction have demonstrated altered clinical parameters, including increased adverse effects, when administered with grapefruit juice. Therefore, it is advisable to avoid this combination, especially with the more affected agents — felodipine, nisoldipine and nicardipine.

CNS modulators
The benzodiazepines are the most important and widely used family of sedative—hypnotics, acting on inhibitory receptors in the CNS. Few of them are CYP3A4 substrates at a certain level, and a potential interaction with grapefruit juice may cause a deviation from the standard dose, producing an undesired increase in the CNS-depressant effects. A single glass of regular strength grapefruit juice has been shown to increase by more than 3-fold the AUC of diazepam (Ozdemir et al, 1998). A similar amount of the juice increased by 50% the AUC, as well as the peak concentration of triazolam and midazolam, two short-acting hypnotics, without affecting the elimination half-life (Hukkinen et al, 1995; Kupferschmidt et al, 1995). A more recent study has shown that repeated consumption of grapefruit juice increases the AUC of triazolam by as much as 150% (Lilja et al, 2000a).
However, grapefruit juice does not alter the pharmacokinetics of alprazolam, even after repeated ingestions, presumably due to its high bioavailability (Yasui et al., 2000). As to the clinical effect, the available data are more ambiguous. A performance decrease in psychometric tests of human subjects undergoing treatment with Midazolam and grapefruit juice compared to water has been observed in one pharmacodynamic study (Kupferschmidt et al., 1995). On the other hand, in a different study, hardly any increase in the clinical effects of midazolam and triazolam has been detected following grapefruit juice intake (Vanakoski et al., 1996). The reported increase in bioavailability of these agents may be clinically significant, especially in patients possessing other risk factors for decreased first pass elimination such as liver disease and old age.

Another CNS depressant showing an interaction with grapefruit juice is the anticonvulsant agent carbamazepine. A 40% increase in carbamazepine AUC was observed after ingestion of a single glass of the juice (Garg et al., 1998).

Grapefruit juice has also been observed to increase substantially the plasma concentration of buspirone, a nonbenzodiazepine hypnotic with a very low bioavailability due to extensive metabolism by CYP3A4 (Lilja et al., 1998). Such a dramatic increase could result in toxic levels of buspirone. Hence, avoiding this combination should be advised.

### Table 1 Summary of drug interaction with grapefruit juice

<table>
<thead>
<tr>
<th>Drug</th>
<th>Grapefruit juice influence</th>
<th>Potential risk</th>
<th>Recommendation</th>
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</thead>
<tbody>
<tr>
<td><strong>Calcium channel antagonists</strong></td>
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<tr>
<td>Felodipine</td>
<td>Increased bioavailability</td>
<td>Hypotension, tachycardia</td>
<td>Avoid combination</td>
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<tr>
<td>Nisoldipine</td>
<td>Increased bioavailability</td>
<td>Hypotension, tachycardia</td>
<td>Avoid combination</td>
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<tr>
<td>Nicardipine</td>
<td>Increased bioavailability</td>
<td>Hypotension, tachycardia</td>
<td>Avoid combination</td>
</tr>
<tr>
<td>Nitrendipine</td>
<td>Increased bioavailability</td>
<td>Hypotension, tachycardia</td>
<td>Avoid combination</td>
</tr>
<tr>
<td>Pranidipine</td>
<td>Increased bioavailability</td>
<td>Hypotension, tachycardia</td>
<td>Avoid combination</td>
</tr>
<tr>
<td>Nimodipine</td>
<td>Increased bioavailability</td>
<td>Hypotension, tachycardia</td>
<td>Avoid combination</td>
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<tr>
<td>Nifedipine</td>
<td>No influence</td>
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<td>None</td>
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<tr>
<td>Amlodipine</td>
<td>No influence</td>
<td></td>
<td>None</td>
</tr>
<tr>
<td>Verapamil</td>
<td>Increased bioavailability</td>
<td>Hypotension, tachycardia</td>
<td>Avoid combination</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>No influence</td>
<td></td>
<td>None</td>
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<tr>
<td><strong>CNS modulators</strong></td>
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<tr>
<td>Diazepam</td>
<td>Increased bioavailability</td>
<td>Increased CNS depression</td>
<td>Avoid combination</td>
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<tr>
<td>Triazolam</td>
<td>Increased bioavailability</td>
<td>Increased CNS depression</td>
<td>Avoid combination</td>
</tr>
<tr>
<td>Midazolam</td>
<td>Increased bioavailability</td>
<td>Increased CNS depression</td>
<td>Avoid combination</td>
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<tr>
<td>Alprazolam</td>
<td>No influence</td>
<td></td>
<td>None</td>
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<tr>
<td>Carbamazepine</td>
<td>Increased bioavailability</td>
<td>Increased adverse effects</td>
<td>Avoid combination</td>
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<tr>
<td>Buspirone</td>
<td>Increased bioavailability</td>
<td>Increased adverse effects</td>
<td>Avoid combination</td>
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<tr>
<td>Sertraline</td>
<td>Increased bioavailability</td>
<td>Increased adverse effects</td>
<td>Avoid combination</td>
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<tr>
<td><strong>HMG coA reductase inhibitors</strong></td>
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<tr>
<td>Simvastatin</td>
<td>Increased bioavailability</td>
<td>Rhabdomyolysis, acute renal failure</td>
<td>Avoid combination</td>
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<tr>
<td>Lovastatin</td>
<td>Increased bioavailability</td>
<td>Rhabdomyolysis, acute renal failure</td>
<td>Avoid combination</td>
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<tr>
<td>Atorvastatin</td>
<td>Increased bioavailability</td>
<td>Rhabdomyolysis, acute renal failure</td>
<td>Avoid combination</td>
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<tr>
<td>Pravastatin</td>
<td>No influence</td>
<td></td>
<td>None</td>
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<td><strong>Immunosuppressants</strong></td>
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<tr>
<td>Cyclosporine</td>
<td>Increased bioavailability</td>
<td>Nephrotoxicity, hypertension, cerebral toxicity</td>
<td>Avoid combination</td>
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<td><strong>HIV protease inhibitor</strong></td>
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<tr>
<td>Saquinavir</td>
<td>Increased bioavailability</td>
<td>Increased adverse effects</td>
<td>Avoid combination</td>
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<tr>
<td><strong>Phosphodiesterase-S inhibitor</strong></td>
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<tr>
<td>Sildenafil</td>
<td>Increased bioavailability</td>
<td>Increased adverse effects</td>
<td>Avoid combination</td>
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<tr>
<td><strong>Antihistamines</strong></td>
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<tr>
<td>Terfenadine</td>
<td>Increased unmetabolised drug in plasma</td>
<td>QT prolongation, torsade de pointes</td>
<td>Avoid combination</td>
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<td><strong>Prokinetics</strong></td>
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<tr>
<td>cisapride</td>
<td>Increased bioavailability</td>
<td>QT prolongation, torsade de pointes</td>
<td>Avoid combination</td>
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<tr>
<td><strong>Antiarrhythmics</strong></td>
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<tr>
<td>Amiodarone</td>
<td>Blockage of Metabolite formation</td>
<td>Arrhythmias</td>
<td>Avoid combination</td>
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</tbody>
</table>
Sertralin is a serotonin selective reuptake inhibitor that is widely used in the treatment of depression and anxiety disorders, and is metabolized mainly by CYP3A4. A 50% increase in the bioavailability of sertralin when given with grapefruit juice has been reported. These results were consistent with *in vitro* inhibition of sertralin metabolism (Lee *et al.*, 1999). The clinical relevance of the interaction has not been assessed.

**HMG-CoA reductase inhibitors**

The statins are an important class of cholesterol lowering medications that act by competitive inhibition of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase. Statins undergo metabolism through CYP3A4 to various degrees. Simvastatin and lovastatin are inactive lactones that undergo hydrolysis by esterases to form the active simvastatin acid and lovastatin acid, respectively. Inhibition of simvastatin metabolism by naringenin was demonstrated *in vitro* (Ubeaud *et al.*, 1999). After drinking 200 ml double-strength grapefruit juice three times a day for 3 days, the concomitant intake caused a 16-fold increase in the AUC of simvastatin, and a seven-fold increase in the AUC of simvastatin acid (Lilja *et al.*, 1998). The same regimen of grapefruit juice caused a 15-fold increase in the AUC of lovastatin, and a five-fold increase in the AUC of lovastatin acid (Figure 2) (Kantola *et al.*, 1998). Although a large amount of grapefruit juice has been used, these data can indicate that a regular amount of the juice can alter the pharmacokinetic parameters of simvastatin and lovastatin. This trend is further supported by double AUC values for lovastatin and lova-statin acid after drinking one glass of regular strength grapefruit juice in the morning for three consecutive days followed by a dose of the medicine at the third evening (Rogers *et al.*, 1999). The AUC value of atorvastatin showed a 2.5-fold increase after drinking double-strength grapefruit juice 3 times a day for 3 days (Lilja *et al.*, 1999). Grapefruit juice has no effect on pravastatin (Lilja *et al.*, 1999), apparently since it is metabolized only to a limited extent by CYP3A4 (Jacobsen *et al.*, 1999). It would be wise to avoid the combination of this class of medications with grapefruit juice, especially in view of the fact that the concomitant intake of statins with CYP3A4 inhibitors produced adverse effects such as rhabdomyolysis and acute renal failure (Williams & Feely, 2002).

**Cyclosporine**

Cyclosporine is a powerful immunosuppressive agent used extensively in transplantation to prevent rejection of transplanted organs. Cyclosporine is extensively metabolized by CYP3A4 in the gut wall of the small intestine and in the liver (Kolars *et al.*, 1991). It is also a high affinity P-gp substrate (Lown *et al.*, 1997). An increase of more than 60% in cyclosporine AUC was reported following grapefruit juice ingestion (Ducharme *et al.*, 1995; Ioannides Demos *et al.*, 1997). This alteration has been observed with the cyclosporine microemulsion formulation as well (Bistrup *et al.*, 2001). Elevated cyclosporine concentrations were reported in healthy subjects (Yee *et al.*, 1995) and in transplant patients (Min *et al.*, 1996). In pediatric renal transplant patients, concomitant grapefruit juice administration altered cyclosporine AUC, $C_{max}$ and elimination parameters as well (Brunner *et al.*, 2000). Grapefruit juice had no effect after intravenous administration of the drug (Ducharme *et al.*, 1995). Cyclosporine has a narrow therapeutic index, and many side effects such as nephrotoxicity, hypertension and cerebral toxicity. Therefore, it seems necessary to advise patients treated with cyclosporine not to consume grapefruit juice during therapy.

**Saquinavir**

Saquinavir is a protease inhibitor, used in the treatment of human immunodeficiency virus infection. It has poor oral bioavailability because of extensive intestinal metabolism, mediated by CYP3A4 (Fitzsimmons & Collins, 1997). The oral bioavailability of saquinavir increased by a factor of two following ingestion of 400 ml grapefruit juice, without

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**Figure 2** Serum concentrations of lovastatin and lovastatin acid after a single oral dose of 80 mg lovastatin, after ingestion of large amounts of grapefruit juice (●) or water (○).
affecting elimination parameters, and with no effect after intravenous administration of the drug (Kupferschmidt et al., 1998). Inhibition of saquinavir metabolism in vitro by grapefruit juice components has also demonstrated (Eagling et al., 1999). Until further investigations, this combination should be avoided. Other protease inhibitors have high bioavailability, thus, interaction with grapefruit juice is unlikely to occur.

Sildenafil
Sildenafil citrate is used for the oral treatment of erectile dysfunction. It acts by enhancing the ability of nitric oxide to inhibit phosphodiesterase type 5. Sildenafil undergoes extensive metabolism through CYP3A4 (Hyland et al., 2001). The ingestion of 250 ml grapefruit juice 1 h before and concomitantly with sildenafil increased the oral bioavailability of sildenafil by 23% (Jetter et al., 2002). One case report indicated a 42% increase in C_{max} but no change in AUC value for 100 mg of sildenafil taken with grapefruit juice (Lee & Min, 2001). Consequently, sildenafil pharmacokinetics becomes less predictable with grapefruit juice, and it is advisable to avoid this combination.

Cizapride
Cizapride, a prokinetic agent, has been used for the treatment of a number of gastrointestinal disorders. CYP3A4 is the primary mode of elimination of cizapride (Bohets et al., 2000). In two different studies, 250 ml of grapefruit juice ingested concomitantly with a 10 mg dose of cizapride caused a 50% increase in the bioavailability of cizapride (Gross et al., 1999; Offman et al., 2001). In another study, high doses of grapefruit juice were used and similar outcomes have been reported (Kivistö et al., 1999). Serious cardiac adverse effects, such as tachycardia, palpitations, QT prolongation and torsade de pointes, have been associated with high plasma concentrations of cizapride, including 80 deaths (Michalets & Williams, 2000). It appears that a clinically significant outcome may arise from the combination of cizapride and grapefruit juice, and avoidance of this combination is recommended.

Terfenadine
Terfenadine is a second generation, non-sedative, selective H_{1} receptor antagonist used in the treatment of many allergic conditions. Terfenadine undergoes nearly complete pre-systemic elimination by CYP3A4 to such a broad extent and rapid kinetics that normally terfenadine cannot be detected in plasma. The antihistaminic activity in vivo has been attributed to its carboxilic metabolites (Yun et al., 1993). High levels of unmetabolized terfenadine are associated with significant cardiotoxicity such as QT prolongation and torsade de pointes (Woosley et al., 1993). Administration of grapefruit juice concurrently with terfenadine significantly elevated terfenadine plasma concentrations (Benton et al., 1996; Clifford et al., 1997). One glass of regular strength grapefruit juice was enough to produce maximum effect on terfenadine pharmacokinetics (Rau et al., 1997). As for cardiac effects, repeated consumptions of grapefruit juice simultaneously to 60 mg terfenadine twice a day for a week resulted in a significant increase in QT interval (Benton et al., 1996; Honig et al., 1996).

A 29-y-old man who had been taking terfenadine twice daily for more than a year, collapsed and died on a day on which he had consumed two glasses of grapefruit juice. His postmortem plasma terfenadine concentration was 35 ng/ml, and the death was attributed by the coroner to terfenadine toxicity. The man was not taking erythromycin, ketoconazole, or any other drug known to affect terfenadine metabolism (Spence, 1997). Thus, it seems necessary to avoid concomitant consumption of grapefruit juice and terfenadine.

Amiodarone
Amiodarone is a class III antiarrhythmic agent. Its major metabolite, N-desethylamiodarone (N-DEA) has been shown to contribute the antiarrhythmic effect, possibly to a greater extent than the parent drug (Talajic et al., 1987; Zhou et al., 1998). Formation of N-DEA is mediated by CYP3A4 (Fabre et al., 1993). A measure of 300 ml grapefruit juice simultaneously, 3 and 9 h after amiodarone dose, caused a complete inhibition of N-DEA formation (Libera et al., 2000). The clinical implications of this finding are still unclear and need further investigation.

Conclusions
It is likely that more information regarding this interaction, including more drugs exhibiting the interaction, will accumulate in the future. It can be anticipated, based on the analogous mechanism, that grapefruit juice will demonstrate, at least partially, similar interactions that occur with erythromycin, ketoconazole and other macrolide antibiotics andazole antifungal agents. It is important to notice that the whole fruit can cause the same outcomes as does the juice (Bailey et al., 2000).

The vast majority of the investigations regarding this interaction are characterized by a wide variability of the results among patients within each study, as well as variability between studies. The different kinds of juice used by different investigators might be a contributor for this. There might be differences in the ability to inhibit the enzyme, between fresh and processed juice, as well as between hand-squeezed vs machine-squeezed, where the machine squeezing can produce a better extraction of the active components. There is no uniformity in the concentrations of the different constituents between different manufacturers, and even between different batches (Fukuda et al., 2000). Hence, the argument that a patient whose
condition is balanced by drug therapy, and drinks grapefruit juice regularly, can safely maintain this habit, seems to be imprudent, and each patient should be considered individually. Furthermore, wide variations in intestinal concentrations of CYP3A4 among individuals contribute to the differences in the intensity of the interaction. CYP3A4 content in the duodenum and jejunum, the more enzymatically active regions of the intestine, have been found to vary by more than 30-fold among 20 patients (Paine et al., 1997). The importance of variability in CYP3A4 content is further established by the reproducibility within patients following repeated testing, implying dependency on factors inherent to the individual (Bailey et al., 1995).

There is a potential therapeutic benefit in using grapefruit active constituents to increase drug bioavailability. A financial opportunity also exists, since lowering the effective dose will reduce drug costs. However, until the active components are fully isolated and defined, and the intensity of the bioavailability increment is well predictable, this exploitation will be unsafe.

An interaction between drug and food or drink might reveal more difficulties than a drug–drug interaction (Spence, 1997). A major difficulty is related to warning the public: while a pharmacist consults the patient before dispensing a medicine, a salesperson is not expected to do so before selling food. It is important that the awareness for this potential food–drug interaction will increase, and actions must be taken in order to prevent undesired and harmful clinical consequences.

References


