Clinical Practice

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Drug Interactions with Grapefruit Juice

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ABSTRACT

Grapefruit juice sales are gradually increasing since 1970s and reached an average of 24.9 million litres per annum between 2004 and 2007. The use of grapefruit juice on its own or in a mixture with other juices is gradually increasing in UK and grapefruit juice is now a regular part of breakfast consumption in most of Western Europe and America.

Since the accidental discovery of its interaction with felodipine, more than 85 drugs have been identified to have the potential to cause serious adverse reactions. However there has been a lack of awareness of its effects on other medications in patients as well as physicians. It is necessary for all medical practitioners to be aware of the potential for enhanced serum levels of the affected drugs and the possibility of serious adverse effects.

Grapefruit juice inhibits the CYP3A4 enzyme of the cytochrome P450 system in the intestinal mucosa, increasing the bioavailability of drugs with a high first pass metabolism. Therapeutic doses of the affected drugs may produce serious adverse reactions. More research is necessary to identify the mechanism of such interactions and to identify the active ingredients.

Introduction

Grapefruit (Citrus paradise) is thought to have originated as a cross between the Jamaican sweet orange (Citrus sinensis) and the Indonesian pomelo (Citrus maxima) fruit. It was first bred in Barbados and brought to Florida in 1820s. Subsequently, different mutant and hybrid varieties were developed. Although the white and pink varieties were being popularly consumed, the ruby red variety has become very popular and commercially successful.

The taste is a mixture of the sweetness and tanginess of an orange and the sourness of a citrus fruit. It is a rich source of vitamins C and potassium. It is found to have antioxidant properties due to the presence of lycopene[1]and an ability to inhibit atherosclerosis due to the presence of pectin[2,3]. The seed extract is thought to have antimicrobial and antifungal properties.

With good publicity, marketing and coverage by health magazines, grapefruit juice has gained widespread use and in most Western Europe and America it is one of the common fruit juices consumed at breakfast. In the United Kingdom, in terms of fruit juice sales, it ranks second among citrus fruits and the fourth overall.[4]

Pharmacokinetic effects

The interaction of grapefruit juice with medication was first reported by Bailey et al in 1991 after their accidental discovery of up to four fold increase in the blood levels of filodipine when taken with grapefruit juice[5]. Further studies have identified similar interactions with more than 85 drugs[6]. The half life of the effects of grapefruit juice is estimated to be around 12 hours[7], but these effects may last from 4 hours to 24 hours[8]. The effects are more pronounced with regular consumption of grapefruit juice prior to ingestion of the drug and there can be a cumulative increase in drug concentrations with continued grapefruit juice intake[7,9].

As little as 200-250ml may be sufficient to induce its effects[,10]. Some of the interactions involve medication that have narrow therapeutic window and can therefore cause potent adverse effects such as torsade de pointes, rhabdomyolysis, myelotoxicity, respiratory depression gastrointestinal bleeding, nephrotoxicity and sudden cardiac death.[6] There is a lack of awareness among both doctors and patients about its effects and interaction with various medications.

Mechanism of action

These pharmacokinetic interactions with grapefruit juice are more observable in drugs with high first pass metabolism and in those with an innate low oral bioavailability. The oral bioavailability of affected drugs is increased but their half life usually remains unaltered[11,12]. Grapefruit juice is associated with the inhibition of Cytochrome P450 enzyme system, particularly the CYP3A4 enzyme[7]. The CYP3A4 enzyme is present both in the liver and intestinal mucosa. Once the drug is taken up by the mucosa, the susceptible drug may be metabolised by the

CYP3A4 or pumped back into the intestine lumen by P-glycoprotein. The observed effects of grapefruit juice are thought to be mainly due to the inhibition of intestinal CYP3A4 activity, which leads to decreased first pass metabolism and hence increased bioavailability. This inhibitory action is fairly quick and may be due to the rapid degradation of the enzyme or any decrease in its production from the mRNA. The production of mRNA itself from DNA is not thought to be affected[13]. The susceptibility varies between individuals depending upon their genetic expression of CYP3A4, the effects being more prominent in those with high small intestinal CYP3A4 content[7, 14].

Table 1: Potential risk of drug interactions with grapefruit juice[6, 7,13,25,26,27]

		Risk of Interaction		
Group	**Drug**	**V High**	**High**	**Mod**
Anaesthetic	Ketamine	+++		
Anaesthetic	Alfentanil		++	
	Fentanyl		++	
Antiarrhythmic	Dronedorone	+++		
	Amiodorone		++	
	Quinidine			+
Anti-Cancer	Dasatanib		++	
	Everolimus		++	
	Nilotinib		++	
	Pazopanib		++	
	Sunitinib		++	
	Vanetanib		++	
Antidepressants	Buspirone		++	
	Sertraline			+
	Clomipramine			+
Antiemetic	Domperidone	+++		
Antiepileptics	Carbamazapine		++	
Anti-HIV	Maraviroc	+++		
	Ripivirine		++	
Anti-infective	Erythromycin		++	
	Quinine		++	
	Primaquine		++	
Antiplatelet	Clopidogrel		++	
Antipsychotics	Pimozide		++	
	Quetiapine		++	
	Ziprasidone		++	
Benzodiazepines	Midazolam			+
	Diazepam			+
	Triazolam			+
Ca-channel bolckers	Felodipine			+
	Nifedipine			+
Immunosuppressants	Cyclosporin		++	
	Tacrolimus		++	
	Sirolimus		++	
Opiods	Oxycodone		++	
	Methadone		++	
Statins	Simvastatin	+++		
	Atorvastatin		++	
Urinary Tract	Solifenacin			+
	Fesoterodine			+
	Darifenacin			+
	Tamsulosin			+

The effect of grapefruit juice on the P-glycoprotein is unclear. The activation of P-glycoprotein pumps the drug back into the intestinal lumen which should reduce bioavailability and similarly the inhibition of P-glycoprotein increases the bioavailability. Some studies suggest that the inhibition of P-glycoprotein is the mechanism responsible for the increased bioavailability of certain drugs like cyclosporine[15,16].

The active ingredients responsible for interactions of grapefruit juice with medication are not clearly identified. The compounds exerting this action are thought to be either the flavanoids such as naringin and naringinen[17,18,19,20] or the furanocoumarins such as bergamottin and its derivatives[21,22,23,24], but there is no clear consensus.

Drug interactions

Table 1 below lists some of the commonly used drugs whose bioavailability is affected by grapefruit juice. Although the best known interactions have been mentioned in the table, there are many other drugs like carvedilol, estrogens, itraconazole, losartan and methyl prednisolone whose bioavailibility is increased by grapefruit juice and the adverse effects are not yet clear.

Implications on clinical practice

Clinicians should make themselves aware and educate their patients of these potential interactions, keeping in mind the individual variations in susceptibility. This may be particularly important for medications that have a very narrow therapeutic window, medication that have an innate low oral bioavailability and a high first pass metabolism mainly via CYP3A4.

A patient may develop exceptional beneficial effects or equally, significant adverse effects should he start consuming grapefruit juice mid- treatment. Conversely, a drop in efficacy of a drug is also possible, should a patient using grapefruit juice on a regular basis, stops it suddenly.

To achieve steady concentration of the medication and avoid such potential effects, it may be best to advise patients to avoid consuming grapefruit juice if there is a potential of interaction. The half life of the effect of grapefruit juice appears to be around 12 hours and therefore, it is advisable to discontinue grapefruit juice 72 hours prior to starting any drug with potential interactions.[8,9]

Due to the prolonged effect of CYP3A4 inhibition which may last up to 24 hours, it is not possible to avoid these interactions by separating the times of drug and grapefruit juice consumption.[8,9]

There is more research needed to clarify the mechanism of action and to determine the active ingredients. The identification of the active ingredient can allow oral administration of drugs that undergo CYP3A4 mediated high first pass metabolism because of which currently, they can only be given systemically.

In light of the possible increase in bioavailability of specific drugs, although it might be possible for patients to use this to their advantage in reducing the dose of their medication under medical supervision, it is perhaps too early to recommend the use of grapefruit juice as an adjunctive or augmentation strategy.

Competing Interests
None declared
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