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DRUG DISCOVERY

Grapefruit: A Nutritional Fruit Fraught with Danger of Severe Drug Interactions

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ABSTRACT

Grapefruit is a common breakfast item, eaten cut up or imbibed as a juice. It is rich in vitamin C and a variety of other vitamins and minerals. It is cardioprotective. However, it also contains which can inhibit the cytochrome P450 3A4 in the liver and the small intestine, allowing increased bioavailability of many commonly used drugs. This can lead to serious overdose effects. This article briefly reviews the drugs prone to this phenomenon. Grapefruit juice should be avoided if these drugs are being taken.

Keywords: grapefruit, drug interactions, CYP3A4

Abbreviations: CYP3A4, Cytochrome P450 3A4, gms, grams

1. INTRODUCTION

The grapefruit is a subtropical citrus fruit known as the shaddock or shattuck until the 19th century. It is a hybrid fruit first bred in the Barbados, (Carrington, 2003) but now enjoying worldwide popularity. Grapefruit and grapefruit juice are commonly served with breakfast. Grapefruit juice is purchased by almost 21% of all households in the United States on a regular basis. The United States produces nearly 40% of the world's supply of grapefruit. (Mertens-Talcott et al, 2006) Other leading producers are China, South Africa and Mexico. Grapefruit has several nutritional qualities including its high content of vitamin C (Fellers et al, 1990). It also contains the cardiovascular beneficial fiber pectin (Cerda et al, 1988) and several phytochemicals including the anti-oxidant lycopene (Lee, 2000). The American Heart Association labels it as a 'heart healthy food due to its anti-atherosclerotic actions. Grapeseed extract has anti-microbial properties (Ignacio et al, 2005, Kawaii et al, 1999). It is estimated that 100 grams of grapefruit contains approximately 32 calories, 8.8 gms of carbohydrates, 1.1 gms of fiber, 0.63 gms of protein, 0.10 gms of fat and no cholesterol. It also contains several minerals and vitamins (USDA).

2. DISCUSSION

Although nutritionally healthy and readily available throughout the world, grapefruit has the potential to interfere with several commonly used prescription drugs. The major concern is its ability to increase the potency of the therapeutic dose, causing severe side effects due to the resultant overdose effect. The serum concentration of drugs like cyclosporine, some calcium antagonists, and the hydroxymethylglutaryl-coenzyme A reductase inhibitors may increase to the tune of 1.5 to 15 fold with an intake of approximately 8 oz, grapefruit juice (Kane et al, 2000). The incriminating chemicals are several furanocoumarins, especially bergamottin and dihydroxybergamottin. These inhibit the isoform CYP3A4 in the small intestine and the liver, (Bailey et al, 2004) thereby interfering with the metabolism of several drugs. The result is an increased bioavailability of these drugs in the blood (Nebert t al, 2002, Slaughter et al, 1995). Since the concentration of furanocoumarins in grapefruit is variable and depends upon the fruit, manufacturing process and storage condtions, (Fakuda et al, 2000, Ho et al, 2000) the inhibitory effect may last as long as 24-48 hours after a single intake of 8 oz of grapefruit juice (Wilkinson, 2005). Grapefruit drug interactions apply to only non-parenteral drugs. Parenterally administered drugs bypass the GI tract and are not affected by drinking grapefruit juice (Bailey et al, 2004, Guthrie et al. 1998).

2.1. Drugs with major interactions

There are more than 85 drugs that may interact with grapefruit, (Seden et al, 2010) and 43 can generate serious side effects (CMAJ, 2013). These include commonly used anti-cancer, anti-infective, anti-cholesterol, cardiovascular, central nervous system, immunosuppressant, gastrointestinal and urinary tract drugs. An alphabetical list of the major drugs affected is as follows,

Alfentanil – oral (analgesia)
Amiodarone (cardiac arrythmias)
Apixaban (anti-clotting)
Atorvastatin (anti-cholesterol)
Cyclosporine (post organ transplant, rheumatoid arthritis, psoriasis)
Dasatinib (chronic myelogenous leukemia)
Domperidone (anti-nausea)
Dronedarone (cardiac arrythmias)
Eplerenone (heart failure)
Erlotinib (non-small cell lung cancer and pancreatic cancer)
Erythromycin (antibiotic)
Everolimus (kidney cancer, immunosuppressant to prevent rejection of organ transplants)
Felodipine (hypertension/angina)
Fentanyl – oral (analgesia)
Halofantrine (malaria)
Ketamine – oral (analgesia, sedative)
Lapatinib (breast cancer)

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Lovastatin (anti-cholesterol)
Lurasidone (schizophrenia/mental health problems)
Maraviroc (HIV)
Nifedipine (hypertension/angina)
Nilotinib (chronic myelogenous leukemia)
Oxycodone (analgesia)
Pazopanib (renal cell carcinoma and soft tissue sarcoma)
Pimozide (schizophrenia/other mental health problems)
Primaquine (malaria)
Quinidine (cardiac arrythmias)
Quinine (malaria)
Rilpivirine (HIV)
Rivaroxaban (anti-coagulant)
Silodosin (prostate hypertrophy)
Simvastatin (anti-cholesterol)
Sirolimus (post organ transplant)
Solifenacin (urinary frequency/incontinence)
Sunitinib (Renal cell carcinoma, imatinib-resistant gastrointestinal stromal tumor)
Tacrolimus (post organ transplant)
Tamsulosin (prostate hypertrophy)
Ticagrelor (platelet inhibitor)
Vandetanib (thyroid cancer)
Vemurafenib (unresectable or metatstatic melanoma)
Ziprasidone (schizophrenia, mania, bipolar disorder)

3. CONCLUSION

Grapefruit and grapefruit products can be part of a healthy diet, providing patients are not taking any medications that have interactions with it. These dangerous interactions can occur even if grapefruit is consumed many hours before taking the medication. Seville oranges, limes and pomelos also contain active furanocoumarins, and can produce the same effects. Patients taking susceptible medications should forgo grapefruit and grapefruit juice or should be treated with an alternate drug.

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