GRAPEFRUIT JUICE – DRUG INTERACTIONS: IMPORTANCE FOR PHARMACOTHERAPY

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GRAPEFRUIT JUICE-DRUG INTERACTIONS: IMPORTANCE FOR PHARMACOTHERAPY (Abstract): In spite of known health benefits of grapefruit juice, its consumption in combination with drugs requires caution. The drugs most susceptible to pharmacokinetic interactions with clinical significance are those with narrow therapeutic index and low bioavailability due to important first-pass metabolism. Most vulnerable populations are elderly, cirrhotics, subjects with genetic polymorphisms and individuals taking other CYP3A4 inhibitors. The major drug classes that have been reported to present interactions with grapefruit juice are antiallergics, antibiotics, antimalaria drugs, anxiolytics, calcium channel blockers, HIV protease inhibitors, HMG-CoA reductase inhibitors; the degree of pharmacokinetic interaction varies among the compounds of the same class. **Key words**: GRAPEFRUIT, PHARMACOKINETIC INTERACTION, BIOAVAILABILITY

Grapefruit juice (GJ) is widely preferred among consumers as it is a good source of vitamin C, beta carotene, lycopene, folate, bioflavonoids, furanocoumarins, potassium and fibers (1).

Epidemiological facts, clinical trials and animal studies provide strong evidence that GJ reduces risk of cardiovascular diseases (2) and some types of cancer (3,4,5,6,7).

In spite of all these health benefits, mixing GJ with drugs needs special caution. GJ is known to increase the oral bioavailability of many CYP3A4 substrates by inhibiting intestinal phase metabolism and by down regulating CYP3A4 in the small intestine (8).

However, recent data indicate that other mechanisms than inhibition of CYP3A4 are involved in GJ - induced pharmacokinetic interactions. GJ also inhibits some drug transporters like P-glycoprotein (P-gp) and Organic Anion Transporting Polypeptides (OATP) (9). This may help to explain the inconsistent data regarding GJ - drugs interactions and the large variability of the aria under curve (AUC) among patients.

The degree of the interaction with an enzyme inhibitor can be assessed based on midazolam effect. The pharmacokinetic interactions are classified as follows:

- weak - less than two fold increase of AUC of midazolam;
- moderate - two to five fold increase of AUC of midazolam;
- strong - more than five fold increase of AUC of midazolam (10).

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The GJ - **calcium channel blocker** interaction has been known since 1989 (11).

The co-administration of GJ with some **dihydropyridine** calcium channel antagonists like felodipine, nifedipine (12), nicardipine (13), nimodipine (14), nisoldipine (15) and nitrendipine (16) leads to increased AUC ranged from 1.5-fold to 4.0-fold. Especially among the elderly, the increased bioavailability is associated with enhanced reduction of both systolic and diastolic blood pressure and increased frequency of vasodilatation--related side events. The interaction between amlodipine and GJ doesn't present clinical significance because amlodipine has high (80%) oral bioavailability (17).

In the **phenylalkylamines** calcium channel antagonists group, verapamil exhibits a weak interaction with GF and a high inter-subject variability. In a study realized by Fuhr, prolongation of PR interval above 350 ms occurred in two of the 24 individuals in the group receiving GJ (18).

In the **benzothiazepine** calcium channel antagonists group, diltiazem has been found to have an increased bioavailability when co-administrated with GJ but these results need further investigation (19).

Carvedilol is a racemic mixture in which nonselective **β-adrenoreceptor blocking** activity is present in the S(-) enantiomer and **α1-adrenergic blocking** activity is present in both R(+) and S(-) enantiomers at equal potency. Carvedilol has an absolute bioavailability of approximately 25%-35% due to a significant stereoselective first-pass metabolism by CYP2D6, CYP2C9 and CYP3A4 enzymes. Following oral administration in healthy subjects, plasma levels of R(+) -enantiomer is 2 to 3 times higher than S(-) -enantiomer. Subjects with genetic polymorphism (poor metabolizers) present almost 3-fold higher plasma concentrations of R(+) -carvedilol and 1.25 - fold higher plasma levels of S(-)-carvedilol compared to extensive metabolizers. Drinking GJ while taking carvedilol may increase side effects of carvedilol and modify the therapeutic activity. In these circumstances, until new data is available, patients with heart failure receiving carvedilol should avoid GJ intake (8).

Losartan - **angiotensin II receptor (type AT1) antagonist** - is an orally active drug that undergoes substantial first - pass metabolism by CYP2C9 and CYP3A4 enzymes. It is converted, mainly to an active carboxylic acid metabolite (E3174) which is 10-40 times more potent than the parent drug. In healthy volunteers, GJ increases significantly the time to losartan appearance in serum and decreases significantly AUC of the E3174 metabolite suggesting loss of drug efficacy (20).

Amiodarone is an **antiarrhythmic** drug which can cause QTc interval prolongation and severe cardiac ventricular arrhythmia - torsade de pointes. Amiodarone is metabolized by CYP3A4 to N-desethylamiodarone - a metabolite with more potent anti-arrhythmic properties. GJ increases the amiodarone plasma concentrations and inhibits almost completely the production of the active metabolite leading to fewer side effects but also to diminished therapeutic action (21).

Even it has good oral bioavailability (which varies widely 45-100% between patients), the antiarrythmic quinidine should not be associated with GJ without cautious risk and benefit assessment. Careful monitoring of this drug is important due to its narrow therapeutic index and similarity in patient response to sub-therapeutic and toxic amounts of the drug.

HMG-CoA reductase inhibitors - a class of lipid-lowering agents - are associated with the increase the risk of myopathy and rhabdomyolysis, particularly in patients taking higher doses.

Lovastatin, simvastatin, and atorvastatin are highly prone to interactions due to their reduced oral bioavailability as a result of

presystemic metabolism by CYP3A4 (22). Two days of pretreatment with 200 ml double strength GJ three times a day (high dose of GJ) increases AUC for lovastatin and lovastatin acid 15- and respectively 5-fold, without influencing the half-life.

Similar results was obtained by Lilja et al. (23) who showed that GJ increased AUC of simvastatin 16-fold and the Cmax of simvastatin acid about 7-fold. When simvastatin is taken 24 hours after ingestion of high dose GJ, the effect on the AUC of simvastatin is only about 10% of the effect observed during concomitant intake of GJ and simvastatin.

In contrast, pretreatment with 200 ml double strength grapefruit juice three times a day for 2 days increased AUC of atorvastatin only 2.5-fold (22). The half-life of atorvastatin increased from 7.8 hours to 13.3 hours (25). Analogous study reported that GJ didn't change AUC of pravastatin.

As fluvastatin has a good oral bioavailability and is predominantly metabolized by CYP2C9, its use together with GJ is not a matter of concern. In patients who consume GJ together with HMG-CoA reductase inhibitors, potential alternative agents are pravastatin, fluvastatin, or rosuvastatin (8).

At therapeutic drug concentration, sildenafil selectively **inhibits phosphodiesterase PDE5** to increase intracellular cGMP concentration in *corpus cavernosa*. At higher drug concentration, the selectivity of sildenafil for PDE5 is lost and other forms of PDE are inhibited, resulting in a generalized increase in intracellular cGMP and systemic vasodilatation. The clearance of sildenafil is reduced in healthy elderly volunteers (over 65 years) and the free plasma concentrations are approximately 40% greater than in healthy younger volunteers (18-45 years). After GJ consumption, the magnitude of sildenafil AUC increase is variable ranging from 0.8 to 2.6. As AUC can increase even more depending on brands, batches and the volume of GJ intake it is recommended that the combination of sildenafil and GJ should be avoided (26). Also, interaction with tadalafil or vardenafil may cause serious systemic vasodilatation especially when combined with a nitrate (8).

Five of twelve drug withdrawals from the market from 1997 and 2002 were caused by pharmacokinetic interactions. **H1-receptor antagonists** astemizol and terfenadine and the gastrointestinal prokinetic agent, cisapride are CYP3A4 substrates; increased concentrations of these drugs due to pharmacokinetic interactions were associated with QT prolongation, torsades de pointes and other ventricular arrhythmia. Severe side--effects were also reported for calcium channel blockers mibefradil and HMG-CoA reductase inhibitor cerivastatin which are also CYP3A4 substrates (27). Ebastine and loratadine, other H1-receptor antagonists, which undergo important first-pass metabolism by CYP3A4 may also present higher concentrations levels after GJ administration. Although the co-administration of loratadine with CYP3A4 inhibitors such as erythromycin, ketoconazole, clarithromycin and cimetidine is associated with increases the loratadine's levels, the prolongation in the QTc interval doesn't occur. The arrhythmogenic potential of the ebastine is higher as it is chemically related to terfenadine.

Special care should be taken into consideration also for psychiatric patients who use drugs with narrow therapeutic index such as tricyclic **antidepressants** (clomipramine) or **anticonvulsivants** like carbamazepine (28). According to Lee et al. (29), GJ increases bioavailability of sertraline with 50%. Regarding **anxiolytics**, in healthy volunteers, midazolam AUC increased with 52% when given with GJ and triazolam AUC with 96% as compared to control group (30, 31, 32). The administration of GJ needs special caution in cirrhotic patients, elderly individuals or subjects taking other CYP3A4

inhibitors. In these patients GJ increased the AUC of midazolam by 106% and decreases the ratio of the AUCs alpha-hydroxymidazolam (metabolite) /midazolam by 85% (33) which may result in excessive sedation and other side-effects. Furthermore, GJ raise dramatically the AUC of non-benzodiazepine anxyolitic buspirone by 9.2 fold (34).

Interesting results are provided by an experimental study which shows that GJ significantly increases the blood concentration of **morphine** in morphine-tolerant rats (35). Also, a clinical trial showed that GJ augments significantly the bioavailability of dextromethorphan with up to three days persistence of the juice impact (36).

Even if GJ almost doubles the AUC for macrolides like clarithromycin the clinical significance of this pharmacokinetic interaction is not relevant (37, 38).

The inhibitory activity of GJ does not always have negative impact as it can also be used to maintain the drug effectiveness. Artemether is a **antimalarial drug** which undergoes high presystemic metabolism by CYP3A4 and presents a high relapse rate during monotherapy (due to autoinduction). GJ increases the oral bioavailability of artemether (39), achieves complete protection of the host from damage induced by schistosomal infection (40) but still cannot prevent the time-dependent reduction in bioavailability.

Halofantrine, another antimalarial drug, presents an oral bioavailability of 10% and is metabolized by CYP3A4 to the less cardiotoxic metabolite, N-debutylhalofantrine. Charbit et al. showed that GJ administration increased halofantrine AUC by 2.8-fold and decreased N-debutyl-halofantrine AUC by 2.4-fold. As GJ prolonged QTc with approximately 82%, this beverage should be contraindicated during administration of halofantrine (41).

Ten years ago a report drew attention to potential fatal interaction between GJ and other drug with narrow therapeutic index – colchicine (an agent used for **gout** treatment) (42). In addition, in Caco-2 cells GJ reduced ratio of basal-to-apical transport to apical-to-basal transport suggesting that, *in vivo,* the bioavailability of this drug might be increased by GJ consumption (43).

Another class of drugs which presents clinically relevant pharmacokinetic interactions with GJ is the **inhibitors of HIV protease** - ritonavir, indinavir, saquinavir, nelfinavir (44). The bioavailability of saquinavir increases twice after GJ consumption (45).

The co-administation of **immunosuppressive** agent cyclosporine (frequently used in the prophylaxis of organ rejection) with GJ increases AUC by 186% as compared with water (46, 47, 48). Also concentration of tacrolimus should be closely monitored when combined with GJ (49).

On the contrary, GJ decreased AUC of the **antineoplasic** agent etoposide with approximately one quarter when administered concomitantly (50). Studies realized on Caco-2 cells indicate that the ratio of basal-to-apical transport to apical-to-basal transport of [3H] vinblastine was reduced by extracts of GJ (51, 52). Further research is needed to underline the clinical significance of this interaction.

Interaction between **hormones** like ethinyl--estradiol (53) or methylprednisolone and GJ can be considered weak and seem to be unlikely to be clinically relevant. It has to be mentioned that a decrease in morning cortisol plasma concentrations has been observed after administration of methylprednisolone with GJ (54,55). Recent data show that regular intake of GJ presents an important impact on the bioavailability of budesonide nearly doubling it (56).

Our data show that, in healthy volunteers, the association of non-steroidal anti-inflammatory drugs like celecoxib or diclofenac with GJ presents a large inter-subject variability. In one subject taking celecoxib, Cmax increased by 3.17 fold and AUCtotal by

1.83 fold. Also, in one case, GJ administration increased Cmax of diclofenac by 3.27 fold and decreased elimination half-life by 2.81 fold.

CONCLUSION

When there is a concern for drug toxicity related to increased plasma drug concentration it is recommended that GJ consumption should best be avoided entirely during pharmacotherapy.

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NOUTĂŢI

COMPUŞI CU ACŢIUNE ANTI-OSTEOPOROTICĂ DIN PLANTE MEDICINALE DIN INDIA

Acest studiu a avut drept scop evaluarea *in vitro* a efectelor osteogenice ale unor plante utilizate în medicina tradiţională indiană în tratamentul fracturilor osoase : *Allophylus serratus* (Roxb) Kurtz (*Sapindaceae*), *Cissus quadrangularis* (*Vitaceae*), *Vitex negundo* (Linn.) (*Verbenaceae*). Din aceste plante au fost izolaţi 14 compuşi. Posibilele efecte osteogenice ale acestor compuşi au fost evaluate *in vitro* pe culturi primare de osteoblaste. 5 dintre compuşii testaţi (rutozida, 6'-O-trans-cinamoil catalpolul, agnuzida, negundozida, luteolina) au determinat o creştere a ratei de diferenţiere a osteoclastelor şi a mineralizării. Rezultatele obţinute justifică utilizarea acestor specii în medicina tradiţională indiană în tratamentul fracturilor osoase (Kumar M, Rawat P, Dixit P et al. Anti-osteoporotic constituents from Indian medicinal plants. *Phytomedicine* 2010 ; 17 : 993-999).

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