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REVIEW

Therapeutics

Interaction of Grapefruit Juice and Calcium Channel Blockers

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Drug–drug interactions are commonly recognized occurrences in the hypertensive population. Drug–nutrient interactions, however, are less well appreciated. The grapefruit juice–calcium channel blocker interaction is one that has been known since 1989. The basis for this interaction has been diligently explored and appears to relate to both flavanoid and nonflavanoid components of grapefruit juice interfering with enterocyte CYP3A4 activity. In the process, presystemic clearance of susceptible drugs decreases and bioavailability increases. A number of calcium channel blockers are prone to this interaction, with the most prominent interaction occurring with felodipine. The calcium channel blocker and grapefruit juice interaction should be incorporated into the knowledge base of rational therapeutics for the prescribing physician. Am J Hypertens 2006;19: 768–773 © 2006 American Journal of Hypertension, Ltd.

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In 1989, it was noted that co-administration of the calcium antagonist felodipine with usual doses of commercially available grapefruit juice substantially decreased the pre-systemic clearance of felodipine. This interaction substantially increased the systemic exposure to felodipine and by this amplified its pharmacodynamic effects.[1,2] This interaction was discovered by coincidence in the course of an ethanol–drug interaction study in which grapefruit juice was used to mask the taste of the ethanol vehicle.[2] This singular observation has fueled a large volume of grapefruit juice–drug interaction research, with in excess of 225 publications involving more than 25 drugs appearing in the scientific literature.[3] This literature has been extensively reviewed, and the reader is directed to several of these reviews for additional information.[4–8] The emphasis in this review will be on the interaction between grapefruit juice and calcium channel blockers (CCB).

Several findings point to grapefruit juice having a principal effect on the intestinal CYP system with a minor effect at the hepatic level. First, medications interacting with grapefruit juice typically are subject to metabolism by the enterocyte CYP3A4 enzyme system. Only the CYP3A isoforms localized to mucosal cells of the small intestine are inhibited by grapefruit juice. Hepatic CYP3A is at best moderately affected by grapefruit juice administration and only with its chronic administration.[9] Second, grapefruit juice increases the area under the plasma concentration time curve, a calculable measure of whole-body medication exposure, with minimal if any change in drug half-life. An interaction involving hepatic CYP3A would be expected to influence drug half-life. Third, in standard dose amounts, grapefruit juice has no effect on the pharmacokinetics of these medications when they are intravenously administered.[4,10]

Action of Grapefruit Juice on Intestinal CYP Enzymes

The effect of some CYP3A4 inhibitors dissipates with repeated administration, because they produce a time-dependent induction of CYP3A4 via up-regulation of CYP3A messenger RNA and protein, which appears not to be the case with grapefruit juice.[11] Grapefruit juice appears to reduce CYP3A4 activity by both reversible (competitive or noncompetitive) and irreversible (mechanism-based or suicide inhibition) mechanisms as well as through a true loss of CYP3A4. The latter mechanism was first detected when it was observed that recurrent ingestion of grapefruit juice selectively decreased enterocyte expression (obtained by small bowel biopsy) of both CYP3A4 and CYP3A5, thereby increasing drug bioavailability.[4,12] This effect was selective in that concentrations of CYP1A1 and CYP2D6 did not fall. Moreover, this phenomenon was reproducible when human cell lines modified to express

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CYP3A4 were exposed to grapefruit juice. The failure of messenger RNA expression to decrease with grapefruit juice would suggest that this process is not transcriptionally regulated. The mechanism of the decrease in CYP3A4 protein likely represents either accelerated protein degradation or reduced messenger RNA translation.

It is not unreasonable to presume that one or more components of grapefruit juice degrade intestinal CYP3A4 enzyme by way of irreversible "suicide" inhibition.[4] Such a hypothesis explains the rapid and sustained onset of CYP3A4 inhibition upon exposure to grapefruit juice. For example, upon ingestion of grapefruit juice intestinal CYP3A4 concentration is reduced by 47% within 4 h, and the bioavailability-enhancing effect of ingested grapefruit juice is sustained for at least 24 h.[13,14] Complete recovery from the grapefruit juice effect may take up to 72 h after the last exposure with a recovery half-life from enteric CYP3A4 inhibition of approximately 24 h.[15] Such a recovery pattern is consistent with the time sequence of enzyme regeneration after irreversible (mechanism-based) inhibition.[16]

Interindividual Variability in the Effect of Grapefruit Juice

The expression of the CYP3A4 enzyme shows striking interindividual variability in both the liver and intestine with as much as an eightfold difference found in its intestinal content.[17] Higher concentrations of CYP3A4 in the intestine, as logic would suggest, correlate with greater first-pass metabolism and lower attainable drug levels for felodipine.[12] Ingestion of grapefruit juice reduces enteric CYP3A4 levels similarly in all subjects irrespective of the tissue CYP3A4 concentrations before ingestion.[12] However, patients with the highest intestinal CYP3A4 concentrations will exhibit the greatest effects from grapefruit juice; a finding that is apparent upon scrutiny of felodipine bioavailability data.[12] Alternatively, felodipine-treated patients with very low CYP3A4 activity should experience a lesser effect on bioavailability from grapefruit juice.

P-Glycoprotein, Organic Anion Transporting Polypeptide, and Grapefruit Juice

Given the overlap in substrate specificity between p-glycoprotein, organic anion transporting polypeptide, and CYP 3A4, grapefruit juice might be expected to interact also with these transporter systems. In fact, in vitro data in intestinal cell monolayer experiments suggests that grapefruit juice activates p-glycoprotein[18] and inhibits multiple oat polypeptides.[19] If relevant effects on p-glycoprotein or oat polypeptides were to be present in vivo, drug bioavailability would be expected to be reduced, thereby partially counteracting the increased bioavailability that arises from inhibition of enterocyte CYP3A4. This concept is supported by the observation that some drugs displaying a reduced grapefruit juice effect are also known substrates for p-glycoprotein.[4,20] However, current information on the in vivo effect of grapefruit juice on CYP3A4, p-glycoprotein, and oat polypeptides is insufficient to make a qualified statement concerning their mutual interactive effect on bioavailability.[21]

Quantity of Grapefruit Juice and Bioavailability Effect

Early studies of this interaction used multiple glasses of frozen juice reconstituted with half the recommended water.[4,5,7] Most of the subsequent studies evaluating pharmacokinetic interactions between drugs and grapefruit juice have been performed using one 200-mL glass of juice, as CYP3A4 is substantially inhibited after ingestion of a single glass of grapefruit juice.[4] For example, one glass of regular-strength grapefruit juice is comparable to two to three glasses of double-strength juice in how the pharmacokinetics of felodipine are influenced.[2,4,22] Daily ingestion of grapefruit juice over several weeks may slightly attenuate the effect of the juice,[12,23] because 24 h after ingestion of a glass of grapefruit juice a 30% residual effect exists.[13,14] Consumption of grapefruit juice in the order of six to eight glasses per day is required if hepatic CYP3A4 is to be inhibited.[24] The lag phase for the effect from grapefruit juice is an additional consideration with this interaction. Rogers et al[24] showed that the daily consumption of a glass of regular-strength grapefruit juice has a minimal effect on plasma concentrations of the 3-hydroxy-3-methylglutary/coenzyme A (HMG-CoA) reductase inhibitor lovastatin (approximately 30% to 40% increase) taken approximately 12 h later; however, the length of a lag phase effect for grapefruit juice is likely to be both compound specific and highly individualized.

Active Constituents of Grapefruit Juice

Soon after the initial report of the grapefruit juice–felodipine interaction, it was shown that other citrus fruit products such as orange juice were not similarly interactive, suggesting that grapefruit juice contained specific causative substances. Many compounds, both flavanoids and nonflavanoids, have been offered as the active inhibitory ingredients in grapefruit juice.[4] The candidate flavanoid compounds have included naringenin, naringin, quercetin, and kaempferol,[25,26] and the nonflavanoid compounds most commonly cited have been bergamottin and 6′, 7′ dihydroxybergamottin.[27,28] Grapefruit contains several flavanoids (mainly as glycosides), which are presumed to be electron-rich substrates for CYP_{450} enzymes that are ultimately hydrolyzed to the corresponding aglycons and sugar by intestinal microflora. Naringin, the glycoside of naringenin, is found in grapefruit juice in concentrations of 450 μg/mL (10% of the dry weight of juice), making it the most abundant flavanoid in grapefruit juice.[4] Naringin is what gives grapefruit juice its distinctive aroma and pungent taste, and it is not found in other citrus or fruit juices. Although naringenin, the metabolite of narginin, is a potent in vitro inhibitor of both the