

Lown et al. (1) report a significant advance in describing a new mechanism by which ingested nutrients may change exposure to drug therapy. Grapefruit juice was reported to increase plasma concentrations of felodipine and nifedipine when the drug was concurrently administered with grapefruit juice (2). The potential clinical importance of such an interaction was noted when cyclosporine A (3) and terfenadine (4) were noted to have decreased oral clearance with concomitant grapefruit juice ingestion. Due to the relatively narrow therapeutic index of each of these drugs, some have expressed concern and the wish to highlight grapefruit juice as a source of risk for some patients. This point of view warrants some discussion.

The mechanism by which grapefruit juice decreases oral clearance of certain drugs is via decreased activity of intestinal cytochrome P-450, specifically the CYP3A isoforms (5). However until the report in this issue of the *Journal*, this had been based on inference from the findings that all drug substrates with oral clearance decreased by grapefruit juice were also CYP3A substrates. Similarly, until the present report, mechanistic studies were oriented toward identification of chemical(s) in grapefruit juice which inhibited CYP3A activity by direct binding to the enzyme. The expected result was that when the appropriate chemical(s) were identified, competitive or noncompetitive inhibition of the enzyme(s) would be demonstrated. Specific components of grapefruit juice which have been studied for CYP3A inhibition include quercetin (6), naringin and naringenin (7), and 6',7'-dihydroxybergamottin (8). Although the current report does not exclude substances in grapefruit juice which directly inhibit the CYP3A enzyme catalytic activity, it rather conclusively demonstrates that an important component of grapefruit juice-mediated decrease in oral clearance of CYP3A drug substrates is a posttranscriptional decrease in the amount of small intestinal CYP3A enzyme. Of course the next step is identification of the mechanism of decreased immunoreactive protein product in the face of unchanged CYP3A4 mRNA. To do this the grapefruit juice component(s) must first be identified, however the task is substantially more complex than simply screening for CYP3A inhibitors. The authors postulate the presence of a mechanism-based, or "suicide" inhibitor of small intestinal CYP3A. A well-described example of such a mechanism is inactivation of specific phenobarbital-inducible hepatic cytochrome P-450 isozymes by chloramphenicol (9). In this instance chloramphenicol is covalently bound as an oxamic acid adduct to an epsilon amino group of a lysine residue of the protein part of the cytochrome P-450 enzyme. In contrast, another well defined mechanism of posttranslational cytochrome P-450 inactivation is that of cAMP-stimulated phosphorylation of specific serine residues of the enzyme apoprotein (10). These mechanisms are distinct from other mechanism-based cytochrome P-450 inhibitors which bind to the heme moiety of the enzyme. This simply points out that there is much work to be done to fully characterize the mechanism of the grapefruit juice effect.

The broader issue is to place grapefruit juice inhibition of oral clearance of CYP3A drug substrates into the context of food-drug, nutrient-drug, and environmental exposure-drug interactions. Such interactions commonly receive initial wide medical and public comment, followed by either incorporation into the knowledge base of rational therapeutics or lapse into obscurity as a forgotten and perhaps trivial footnote. For example, it is widely appreciated that cigarette smoking increases the clearance, therefore the dose requirements, of theophylline due to the somewhat selective induction of CYP1A2 (11). An environmental exposure, that of influenza vaccination for influenza infection, was noted to increase the anticoagulant effect of warfarin, the basis of which is uncertain but probably not decreased clearance of warfarin (12). This potential for interaction and drug toxicity has been somewhat quantified and is generally appreciated in the clinical community. In contrast there is less appreciation that high protein diets may increase clearance of theophylline by 30–40% while high carbohydrate diets may decrease it by 30–40% (13). Similarly, animal studies indicated that ingestion of brussels sprouts or cabbage increases clearance of an oral anticoagulant and clinical study demonstrated that ingestion of charcoal-broiled beef increased oral clearance of phenacetin (14). After a brief flurry of interest in the research, clinical, and public arenas, findings of these food interactions have never been expanded to widely used drugs with narrow therapeutic margins.

With this background, what are the criteria that help one place a "new" food-, nutrient-, or environmental-drug interaction into an appropriate context? First, the extent of the interaction should be considered. Cigarette smoking can increase theophylline clearance and therefore dose requirement severalfold. In contrast, change in dietary protein or carbohydrate is much less, though statistically significant. Associated with this, the site of the interaction should be considered. A gut wall interaction with drugs which undergo substantial gut wall biotransformation is particularly susceptible to food/nutrient interaction as the local concentration of both food/nutrient and drug may be extremely high at the gut wall. Second, of course, the therapeutic margin of the interacting drug(s) must be considered. The literature is replete with diazepam interactions of all types, however, the broad therapeutic index of diazepam almost precludes the possibility of clinical significance. In contrast, triazolam or midazolam, with extensive gut wall CYP3A presystemic clearance and less wide therapeutic index, may be susceptible to more clinically important interactions. Third, in general an inhibitory interaction is accorded greater importance than an inductive interaction. Though loss of therapeutic effect may be of substantial importance in selected instances (e.g., oral contraceptive steroids, oral anticoagulants), more often unexpected excessive drug effect is accorded greater importance. Finally, the amount of food/nutrient or exposure required for an interaction to occur is of importance to ascertain clinical importance of a research observation. In the case of dietary protein-induced increase in theophylline clearance, the finding was made when 44% of total caloric intake was protein, in contrast to the usual diet which contains ~15% protein in the total caloric intake. Therefore, the interaction would be even less during ingestion of a more realistic diet.

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Using these criteria, where does grapefruit juice fit? It moderately decreases oral clearance of CYP3A substrates, some of which have a relatively narrow therapeutic index. It is an inhibitory interaction which may result in increased drug effect/toxicity at a given drug dose. However, the findings are best demonstrated when 240 ml (~ 8 oz) of double-strength reconstituted grapefruit concentrate is ingested simultaneously with the drug substrate (4), or in the present report 8 oz of regular strength grapefruit juice ingested three times daily (1). It is fair to say this is a substantial grapefruit juice exposure that would occur only during unusual dietary circumstances. Therefore, I conclude that the clinical importance of potential grapefruit juice–drug interactions is quite limited. Instead, as demonstrated in the current report, it may give the opportunity for new understanding of mechanisms by which gut wall CYP3A activity can be modulated. It should provide the impetus for further mechanistic study of posttranscriptional and transcriptional regulation of CYP3A isoforms as they relate to “first-pass” clearance after oral CYP3A drug substrate administration.

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