Grapefruit juice–drug interactions


Author’s commentary

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Although in our review article in the British Journal of Clinical Pharmacology we outlined the concept and conduct of the research and the assessment of the unexpected findings that had led us to discover drug interactions with grapefruit, we did not mention the reactions to our results. Swaying scholars to subscribe to the soundness of our science was a hard sell at the start. I can safely say that there was substantial scepticism when our slides were first scrutinized at a national meeting in Canada in 1989. Moreover, the connection with grapefruit encouraged comical comments. Scrutineers of our subsequent manuscript were stupefied. The work was either a humorous hoax or an astute observation. The editor of one major medical journal was mystified. After 6 months of ambivalent argument, we reluctantly retracted the manuscript and resubmitted it to The Lancet. After 2 weeks, I telephoned to confirm that the paper was being processed, and was given the invigorating information that it had already been accepted[1].

The discovery of this interaction illustrated the importance of openness to innovative ideas in research. Grapefruit may have been the first food reported to alter drug metabolism in humans. It inhibited cytochrome P450 3A4 (CYP3A4), indicating that the biotransformation of a broad battery of medications could be affected. The mechanism involved irreversible enzyme inactivation, which appeared innovative. Intestinal CYP3A4 was primarily inhibited, encouraging early endorsement of the gastrointestinal tract as a central site of drug metabolism. Acceptance of our findings stimulated scientists to pursue further studies, including appraisal of possible active ingredients of grapefruit (naringin, furanocoumarins), the actions of related citrus fruits (Seville oranges and limes), and the involvement of other imperative intestinal molecular mechanisms that modulate drug disposition (P-glycoprotein, organic anion transporting polypeptides)[2–4].

Drug interactions with grapefruit are clinically important. A judicious volume of juice, ingested even many hours beforehand, can substantially boost oral drug availability. Accordingly, advocating avoidance of grapefruit during therapy with drugs that are metabolized by CYP3A4 is the only unambiguous way to address clinical concerns about drug toxicity. Particularly problematic are CYP3A4 substrates with serious adverse effects, such as torsade de pointes or rhabdomyolysis, whose therapeutic index is narrow, or whose systemic availability is perceptibly increased by grapefruit. Furthermore, folks over 50 years of age are prime purchasers of grapefruit and the drugs that it affects, giving an expectation of extensive concomitant exposure and the potential for frequent unwanted drug interactions. Nevertheless, there is a paucity of published papers[5]. Health foods, including grapefruit, are regarded as advantageous and innocuous to human health, and practitioners and patients may not deem diet to be dangerous during drug therapy. Unless there is recognition of a reasonable causal relation between an observed undesired drug response and consumption of a dietary constituent, consumers will not make the connection. Hence, health-care professionals should be alert...
to abrupt alterations or persistent unpredictability in the clinical effects of a medication as a possible consequence of diet. Rather than trying to change the regimen, a more apt approach might consist of carefully acquiring a dietary history and abolishing the suspected causative food.

References


Independent commentary

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In 1989, David G. Bailey and his co-authors reported their chance finding that grapefruit juice is not only a bittersweet nutritional loved by some and disliked by others, but also has a pronounced inhibitory effect on drug metabolism [1]. A systematic evaluation of the effects of grapefruit juice on felodipine and nifedipine pharmacokinetics [2] was followed by a flurry of similar grapefruit juice interaction studies and studies of the mechanism and the pharmacodynamic consequences of the interaction. In their subsequent paper in the British Journal of Clinical Pharmacology, they summarized and evaluated the results of these studies.

The grapefruit juice effect is interesting because it occurs with grapefruit and some other citrus fruits, such as tangerines, but not with oranges; only some drugs are subject to metabolic inhibition; and the effect can be very pronounced, causing more than a five-fold increase in the concentrations of some drugs. The explanation for the interaction is that grapefruit juice inhibits the activity of the cytochrome P450 enzyme CYP3A4 in the intestinal mucosa [3], most probably by covalent binding of furanocoumarin metabolites produced by the enzyme. Thus, there is reduced first-pass metabolism mediated by CYP3A4 in the gut wall, with scavenging of the putative inhibitors by the gut wall to avoid inhibition of hepatic metabolism. The practical importance of this is highlighted by the inclusion of information on interactions with grapefruit juice in the package inserts of many drugs that are substrates of CYP3A4.

Because gut wall first-pass metabolism can considerably limit the systemic availability of a drug and contribute to variability in that availability, many researchers expected that the grapefruit juice effect could be exploited to achieve higher and more reproducible concentrations of orally administered drugs that are substrates of CYP3A4. Consequently, start-up companies were founded to benefit from this mechanism. However, the only commercial drugs for which inhibition of intestinal (and, in this case, also hepatic) CYP3A4 has been used extensively to obtain higher and more steady concentrations is the combination of antiretroviral drugs with small doses of ritonavir (so-called 'boosting'). It was also disappointing that interindividual variation in the pharmacokinetics of CYP3A4 substrates was essentially unchanged by co-administration with grapefruit juice [4].

More recent studies have shown that the mechanism of grapefruit juice interaction is more complex [5, 6]. Several moieties in the juice cause substrate-dependent competitive and/or mechanism-based inhibition of CYP3A4 and also inhibit various transporters, including P-glycoprotein and organic anion transporting polypeptides. It remains to be seen whether benefits in drug therapy can be achieved from the application of this information.
Bailey and his colleagues were lucky to observe the grapefruit juice effect, but had the perciption to recognize that their finding was peculiar, the ability to assess the effect in detail, and the patience to contribute to elucidation of the mechanism. They therefore identified an important source of pharmacokinetic variability, detected a new mechanism of drug interactions, and provided a tool for the better understanding of CYP3A4-based first-pass metabolism in the gut wall. On the occasion of the thirtieth anniversary of the *British Journal of Clinical Pharmacology*, I should like to congratulate the authors for their achievements and the *Journal* for having published this important paper.

References


