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EDITORIALS

Drug-grapefruit juice interactions

Two mechanisms are clear but individual responses vary

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Grapefruit juice, which is widely consumed for its positive health benefits, can have severe, sometimes fatal, interactions with drugs. This phenomenon was first identified serendipitously about 20 years ago for the calcium channel antagonist felodipine,[1] and a recent review found that more than 85 drugs can be affected by grapefruit juice.[2] Two main mechanisms, which have different clinical consequences, have been defined (table⇓).

Firstly, grapefruit juice contains furanocoumarins (such as 6′,7′-dihydroxybergamottin),[3] which can cause irreversible inhibition of the cytochrome P450 enzyme, CYP3A4, mainly in the small intestine.[4] CYP3A4 is involved in the metabolism of around 50% of drugs, so a wide variety of drugs can be affected by the consumption of grapefruit juice. The net effect is a reduction in the pre-systemic metabolism of these drugs, which increases their systemic exposure, sometimes by more than 700% (as has been shown for simvastatin).[5] Because inhibition of CYP3A4 is irreversible, it can last for longer than three days after ingestion of grapefruit juice, until new enzyme has been synthesised in the gut wall.[2]

The interaction can occur after ingestion of freshly squeezed juice, juice from concentrate (as little as 200 mL), and consumption of the fruit itself.[5] The effect on drug pharmacokinetics seems to be greater with regular consumption. The clinical consequences can vary from an asymptomatic increase in drug concentrations to life threatening events.[2 5] Such a life threatening event is described in a case report of impaired metabolism of amiodarone after ingestion of grapefruit juice that led to an increase in QT interval and torsades de pointes.[6] Similarly, rhabdomyolysis has been described after co-ingestion of grapefruit juice with atorvastatin.[7]

A second mechanism involves the inhibition of a member of the influx transporter protein family (organic anion transporter polypeptide; OATP) by grapefruit.[8] Flavonoids such as naringin and hesperidin have been implicated in the mechanism of OATP inhibition. The net effect is reduced bioavailability of the drug, with a decrease in its systemic and tissue concentrations and thus a decrease in its efficacy. In contrast to the effect of grapefruit juice on CYP3A4, the inhibition of OATPs shows a clear volume (dose)-response association, which is competitive in nature, with inhibition lasting about four hours. Thus, a simple way to avoid this interaction is to have a four hour gap between the intake of grapefruit juice and drug administration.[8] Drugs affected through this mechanism include aliskiren, celiprolol, fexofenadine, and ciprofloxacin.

The clinical consequences of both types of interaction are difficult to predict for individual patients. Sequelae depend on the bioavailability of the drug, the intrinsic level of expression of CYP3A4 or OATPs in the gut, the amount and frequency of grapefruit juice consumption, and the characteristics of the grapefruit juice ingested (fruit species, geographical origin, maturity, manufacturing processes, storage conditions, and seasonal variability).[2 5 8] The first of the two mechanisms is most important clinically because of the serious toxic effects that can arise with certain drugs and because the inhibition is irreversible. It is therefore important to ask patients about consumption of grapefruit juice, to document this in the clinical notes, and to provide information on avoiding grapefruit juice, particularly if drugs have a narrow therapeutic index or toxic manifestations that can be severe. For some drugs that are known to interact with grapefruit juice, it has been proposed that the dose given may be reduced; however, it is difficult to predict the consequences of an interaction for different people taking the same drug.[2] Thus, it is probably wise to prescribe an alternative drug that is not affected by grapefruit juice consumption.

The table lists the commonly used drugs that are affected by grapefruit juice, but many other drugs can also be affected. Further information can be obtained from other sources such as the *British National Formulary* (appendix 1). More research is needed to define which other drugs currently on the market can be affected by grapefruit juice, and to develop better methods to assess the severity of the interaction for different people. Efforts to reduce the furanocoumarin content of grapefruit juice are also under way through crossbreeding,[9] alternative processing techniques,[10] and the use of edible fungi.[11]

Finally, although this editorial has focused on grapefruit juice, furanocoumarins are also present in Seville oranges and pomelos. Furthermore, other fruits and juices, including cranberry, Goji berry, and apple, contain other active moieties that can affect different P450 isoforms and transporters and interact with different drugs. It is therefore important to take a careful dietary history from patients and provide them with the

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relevant information to minimise the effects of these potentially serious interactions.

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1 Bailey DG, Spence JD, Munoz C, Arnold JM. Interaction of citrus juices with felodipine and nifedipine. *Lancet* 1991;337:268-9.
2 Bailey DG, Dresser G, Arnold JM. Grapefruit-medication interactions: Forbidden fruit or avoidable consequences? *CMAJ* 2012; published online 26 Nov.
3 Paine MF, Widmer WW, Hart HL, Pusek SN, Beavers KL, Criss AB, et al. A furanocoumarin-free grapefruit juice establishes furanocoumarins as the mediators of the grapefruit juice-felodipine interaction. *Am J Clin Nutr* 2006;83:1097-105.
4 Lown KS, Bailey DG, Fontana RJ, Janardan SK, Adair CH, Fortlage LA, et al. Grapefruit juice increases felodipine oral availability in humans by decreasing intestinal CYP3A protein expression. *J Clin Invest* 1997;99:2545-53.
5 Seden K, Dickinson L, Khoo S, Back D. Grapefruit-drug interactions. *Drugs* 2010;70:2373-407.
6 Agosti S, Casalino L, Bertero G, Barsotti A, Brunelli C, Morelloni S. A dangerous fruit juice. *Am J Emerg Med* 2012;30:248.e5-8.
7 Mazokopakis EE. Unusual causes of rhabdomyolysis. *Intern Med J* 2008;38:364-7.
8 Dolton MJ, Roufogalis BD, McLachlan AJ. Fruit juices as perpetrators of drug interactions: the role of organic anion-transporting polypeptides. *Clin Pharmacol Ther* 2012;92:622-30.
9 Greenblatt DJ, Zhao Y, Hanley MJ, Chen C, Harmatz JS, Cancalon PF, et al. Mechanism-based inhibition of human cytochrome P450-3A activity by grapefruit hybrids having low furanocoumarin content. *Xenobiotica* 2012;42:1163-9.
10 Cancalon PF, Barros SM, Haun C, Widmer WW. Effect of maturity, processing, and storage on the furanocoumarin composition of grapefruit and grapefruit juice. *J Food Sci* 2011;76:C543-8.
11 Myung K, Narciso JA, Manthey JA. Removal of furanocoumarins in grapefruit juice by edible fungi. *J Agric Food Chem* 2008;56:12064-8.

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Table

Table 1| Drug interactions with grapefruit juice[28]

Mechanism	Site of action	Protein affected	Mechanism of interaction	Effects of interaction	Examples of drugs affected
1	Intestinal wall	Inhibition of cytochrome P450 3A4 (CYP3A4)	Irreversible inhibition; non-competitive; long lasting (>3 days)	Decreased presystemic metabolism; increased drug bioavailability; drug toxicity	Anticoagulants (apixaban, rivoraxaban); antiarrhythmics (amiodarone, propafenone, dronedarone); calcium channel blockers (verapamil, amlodipine, felodipine, nifedipine, nicardipine); drugs that act on the central nervous system (carbamazepine, pimozide, quetiapine, buspirone, triazolam); cytotoxics (nilotinib, sunitinib, lapatanib); immunosuppressants (ciclosporin, tacrolimus, sirolimus); statins (atorvastatin, simvastatin)
2	Intestinal wall	Inhibition of organic anion transporter polypeptides	Reversible inhibition; competitive; short lasting (~4 hours)	Decreased absorption; decreased drug bioavailability; lack of drug efficacy	Aliskiren, celiprolol, fexofenadine, talinolol