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Editorial commentary

Stereoselective interaction of manidipine and grapefruit juice: a new twist on an old tale

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The paper by Uno *et al.* [1] in this issue of the Journal shows that another calcium channel blocker, manidipine, interacts with grapefruit juice and that the interaction is stereoselective. As most of the 1,4-dihydropyridine calcium channel blockers are metabolized by cytochrome P450 (CYP) 3A4, it is not surprising that grapefruit juice should inhibit the intestinal metabolism of manidipine. The important scientific implication of this report is the novel finding that the degree of interaction varies for the two enantiomers of manidipine.

Grapefruit juice interactions

The chance finding some 15 years ago that grapefruit juice but not orange juice increased the bioavailability of felodipine and to a lesser extent nifedipine [2] spawned a new area of research which has resulted in the identification of many grapefruit juice–drug interactions [3]. The finding led to a series of elegant studies to identify the mechanisms [4] and the components of grapefruit juice which might be responsible [3]. The effects seemed to be specific to grapefruit juice until Seville orange juice was found to produce similar changes in the pharmacokinetics of felodipine, suggesting the action was through common constituents of the furocoumarins bergamottin and 6′,7′-dihydroxybergamottin [5].

The main action of grapefruit juice is to produce mechanism-based irreversible inactivation of intestinal CYP3A4, resulting in reduced presystemic metabolism and increased oral bioavailability of drugs which show a high degree of metabolism through this pathway [6]. The recovery of intestinal CYP3A4 activity after a normal single exposure to grapefruit juice has a half-life of about 24 h and is complete within 3 days [7]. Very large doses of grapefruit juice might also inhibit hepatic CYP3A4 [8]. Enhanced oral drug bioavailability could also occur through inhibition of P-glycoprotein reducing intestinal efflux transport but the effects of grapefruit juice on P-glycoprotein have been more controversial [9]. This mechanism may be due to a different constituent specific to grapefruit juice, which could account for grapefruit juice, but not Seville orange juice, causing an increase in the bioavailability of ciclosporin [5]. However, with digoxin, which is considered to be a P-glycoprotein substrate with negligible metabolism, grapefruit juice had little effect on the pharmacokinetics [10], possibly because P-glycoprotein does not contribute extensively to the oral bioavailability of digoxin [9].

Fexofenadine, another P-glycoprotein substrate, taken with grapefruit juice showed an unexpected markedly decreased area under the plasma concentration–time curve (AUC) and peak plasma drug concentration (C_{max}) and there was no change in t_{max} or $t_{1/2}$, suggesting reduced bioavailability rather than increased systemic elimination [11]. This effect was also seen with orange juice and apple juice and was attributed to inhibition of intestinal uptake transport organic anion transporting polypeptides (OATPs) by some constituents of these juices [11, 12]. The β-adrenergic receptor antagonist talinolol is also a P-glycoprotein-transported drug but its bioavailability was also decreased by grapefruit juice, possibly through inhibition of OATPs or other uptake transporters [13]. Thus, the initial understanding that the action of grapefruit juice is through inhibition of intestinal CYP3A4 is not complete and more meticulous

mechanistic studies are required to identify the complex effects. Clinicians should always be vigilant concerning possible interactions.

Have these findings with grapefruit juice opened a Pandora's box of important interactions between drugs and food constituents or are these just trivial effects of purely academic interest [14]? These interactions may be clinically relevant with many commonly used drugs. With the 1,4-dihydropyridines felodipine, nicardipine, nifedipine, nisoldipine and nitrendipine, concomitant grapefruit juice may result in excessive vasodilation with symptoms of flushing, tachycardia or symptomatic hypotension. With the HMG-CoA reductase inhibitors atorvastatin [15], lovastatin [16] or simvastatin [17], taking grapefruit juice with a high dose of these drugs may increase the risk of rhabdomyolysis. Whilst there may be no published case reports of this adverse interaction, it could well have gone unrecognized and there are a number of reports of drug interactions with statins causing rhabdomyolysis when given with other drugs which are perhaps more potent inhibitors of CYP3A4 in the gut and liver [18]. The current trend to more aggressive lipid-lowering therapy with higher doses of statins [19] may be likely to increase this risk. With other drugs with a relatively narrow therapeutic index such as ciclosporin [20, 21] or terfenadine [22], the interaction with grapefruit juice may be even more serious and potentially fatal [23]. Fortunately, interactions with digoxin [10] and warfarin [24] do not appear to be of clinical concern at this moment, but stereoselective and genotype-dependent studies have not been performed, so it is important to remain vigilant.

Furthermore, the elderly may be at particular risk. They are more often prescribed medications and, if they consume grapefruit juice, the interaction may be pronounced and unpredictable with normal dietary amounts of the juice [25].

Food–drug and herb–drug interactions

New interactions are being discovered between drugs and food constituents or with herbal products with increasing frequency. An obvious example is St John's Wort, which reduces plasma concentrations of many drugs by inducing the intestinal P-glycoprotein MDR-1 gene and increasing intestinal and hepatic CYP3A4 activity [26] through activation of the pregnane X receptor [27]. As with grapefruit juice, the interactions between drugs and other phytochemicals in foods or herbal treatments may be very complex. We recently found that multiple doses of an extract of *Ginkgo biloba* reduced plasma concentrations of omeprazole by increasing oxidative metabolism of omeprazole through CYP2C19 and the effect was genotype dependent, being greater in the CYP2C19 poor metabolizers [28]. Genotype-dependent drug interactions with grapefruit juice are also possible, as there are common polymorphisms in the MDR-1 and OATP genes. These polymorphisms have different frequencies in different populations which could result in ethnic differences in the incidence of interactions. The frequency and type of herbal products used in different populations also vary considerably. The concomitant use of herbal medicines and conventional drugs is common in Chinese populations such as that in Hong Kong [29, 30].

Stereoselective metabolism

Stereoselectivity in the pharmacokinetics of many of the calcium channel blockers has also been recognized for many years [31]. Effects of inhibition of stereoselective metabolism with grapefruit juice have been studied before with nicardipine [32], nitrendipine [33] and with amlodipine, which, like other 1,4-dihydropyridines, is a substrate for CYP3A4 but, in contrast, has little presystemic metabolism with an absolute bioavailability of >80%. No effect was seen with either enantiomer of amlodipine [34], although other researchers have suggested there may be differences in this effect between individuals [35] as an earlier study had shown small increases in C_{max} and AUC of racemic amlodipine when taken with grapefruit juice [36].

In the current study [1], the greater effect of grapefruit juice on the less potent (*R*)-enantiomer of manidipine might be predictable considering that it shows the greater presystemic metabolism. Moreover, the prediction of the pharmacodynamic consequences may not be improved much by recognizing the effects on stereoselective metabolism of enantiomers compared with the racemic drug. So is this more detailed information on the effects of grapefruit juice on enantiomers clinically important? For manidipine it may not have great consequence, but for other drugs which have enantiomers with different pharmacological activities it may be more significant. For example, with carvedilol, which may interact with grapefruit juice [9], the β-adrenergic receptor blockade is found only with the (*S*)-enantiomer, but the α-adrenergic receptor blockade is found in both the (*S*)- and (*R*)-enantiomers [37], so alteration of the stereoselective metabolism may alter the ratio of α- to β-adrenergic blockade, which could potentially result in adverse effects which would be difficult to predict from studies measuring only the racemic drug concentrations.

This study clarifies the interaction between the manidipine enantiomers and grapefruit juice. In the field of food–drug and herb–drug interactions there is still much

we need to know. Continued efforts in pharmacovigilance to identify unexpected interactions and clinical pharmacology studies of interactions at an early stage in the development of new drugs and in those already marketed are clearly needed to reduce patient risk.

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