

Grapefruit Juice and Medications

The following information is sourced directly from the Adverse Drug Reactions section of the Therapeutic Goods Administration within the Department of Health and Aging. The information below is intended for use by health professionals.

If you have any questions regarding grapefruit juice and medications seek advice from your health care provider.

For more information visit: <http://www.tga.gov.au/adr/aadrb/aadr0304.htm>

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Interactions with grapefruit juice - amendment

Following comments received after publication of its recent article '[Interactions with Grapefruit Juice](#).¹ ADRAC has re-evaluated the literature, and wishes to revise its advice. Although there are no case reports of significant clinical problems occurring when grapefruit juice and medication ingestion have been separated by more than a few hours, studies suggest there is a potential for grapefruit juice to have an interacting effect for up to 3 days after ingestion, particularly with daily consumption. ADRAC now considers that the safest course is to avoid grapefruit and its juice altogether when taking medicines that interact.

Reference:

1. ADRAC. Interactions with grapefruit juice. *Aust Adv Drug React Bull* 2002;21:14

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Interactions with grapefruit juice

The serendipitous discovery in 1991 of the interaction of grapefruit juice with drugs occurred when grapefruit juice was used to mask the taste of ethanol in a study testing an interaction between the dihydropyridine calcium channel blocker felodipine and ethanol.¹ It is now known that grapefruit juice can interact with a number of drugs, the basis of the interaction being the local inhibition of one of the cytochrome P450 enzymes (CYP3A4) and P-glycoprotein (Pgp) in enterocytes in the intestinal wall.² It has been shown that grapefruit juice *does not affect* hepatic CYP3A4.

Interactions with grapefruit juice have been most frequently studied with the dihydropyridine calcium channel blockers (CCBs) including felodipine and nifedipine. Significant interactions have also been found for some of the HMG-CoA reductase inhibitors (statins), particularly simvastatin but possibly also atorvastatin; the benzodiazepines midazolam and triazolam; as well as cyclosporin, saquinavir, and cisapride. This is not an exhaustive list and there are a number of other drugs with a potential for interaction which have not been studied. A recent article in the *Australian Prescriber* contains a more comprehensive list.³ The two most important characteristics of the "target" drugs are metabolism by gut wall CYP3A4 and/or Pgp and associated low oral bioavailability.

ADRAC has received 14 reports describing possible interactions with grapefruit juice. Most have involved either the dihydropyridine CCBs (5) or statins (5). Three of the reports with CCBs have involved amlodipine, an interaction which is usually considered clinically insignificant. Grapefruit juice can inhibit the metabolism of target drugs and increase the amount of parent drug available for absorption, which may result in an increase in its pharmacological or toxic effects. For the CCBs, the reports usually describe hypotension and related symptoms, and for the statins, most reports describe myalgia and associated effects.

Prescribers should be aware that there are several groups of drugs that may interact with grapefruit juice and patients taking these drugs should be made aware of the possibility. It should also be noted that problems can arise from whole grapefruit (as in four of the ADRAC reports), and that the extent of the interaction can vary with different brands and strengths of juice. It is believed that with the exception of bitter Seville oranges, the interaction does not occur with other citrus fruits.

Options for discussion with patients include:

- Avoid grapefruit juice all together
- Take medication with grapefruit juice every day (with dose adjustment if necessary)
- Separate grapefruit juice and medication by a minimum of 2 hours

References

1. Bailey DG, Spence JD, Munoz C, Arnold JMO. Interaction of citrus juices with felodipine and nifedipine. *Lancet* 1991; 337: 268-269.
2. Bailey DG, Malcolm J, Arnold O, Spence JD. Grapefruit juice-drug interaction. *Br J Clin Pharmacol* 1998; 46: 101-110.
3. McNeece J. Grapefruit juice interactions. *Aust Prescr* 2002; 25: 37 (comprehensive table available at www.australianprescriber.com)