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# 2

## Grapefruit juice can cause drug toxicity

As every clinician knows, the small intestine is not just a passive membrane. A major part of its complex function is the active absorption of nutrients, salts and some vitamins. What many people still don't know is that the small intestine also has a powerful drug-metabolising mechanism whose evolutionary function was to detoxify poisonous materials ingested with food, preventing their absorption and rendering them harmless. This mechanism includes enzymes identical to the drug-metabolising liver enzymes – the so-called cytochrome P<sub>450</sub> oxidase system (of which more in Chapter 9).

Unfortunately for the prescriber, these enzymes in the intestinal mucosa also metabolise and render impotent many important modern drugs, of which the left column of Table 2.1 is a major sample. Drug companies are well aware of this, and set the standard dose of the drugs shown in Table 2.1 up to double the dose that would be adequate were the intestine devoid of metabolic function. So what is the problem? It is that a single glass of grapefruit juice, half a grapefruit or a Seville-type (bitter) orange

irreversibly blocks the intestinal  $P_{450}$  enzymes for up to 24 hours. During that period, up to double the correct dose of the drugs in Table 2.1 may be absorbed into the circulation. This may lead to toxic concentrations in the tissues. Note that it doesn't matter at what time the grapefruit juice is consumed – the intestinal metabolic enzymes will be 'knocked out' for 24 hours. Some authorities, who should know better, suggest that a litre of grapefruit juice must be consumed to cause this effect. This is not so – a 250-ml glass is enough to affect the intestinal enzymes as described.

**TABLE 2.1** Drugs whose absorption is enhanced by a glass of grapefruit juice, a helping of grapefruit or a Seville (bitter) orange

Drug(s) or drug group	Result of enhanced absorption
Calcium-channel blockers – all except diltiazem	Hypotension with all. Risk of heart block and heart failure as well, with verapamil
amiodarone (see Chapter 3 for its many risks)	Risk of circulatory collapse and hepatic toxicity. See <i>BNF</i>
simvastatin and atorvastatin	Increased risk of liver toxicity and side-effects
All erection-enhancing drugs	Hypotension, priapism and other side-effects
Immunosuppressants – ciclosporin, sirolimus and tacrolimus	Irreversible rejection of grafted tissue
Antivirals – efavirenz and saquinavir	Failure to control the infection
warfarin	Enhanced anti-coagulation and its risks
The anxiolytic buspirone	Excessive and prolonged sedation
carbamazepine	Risk of blood, liver and skin disorders (see 24 lines of side-effects in <i>BNF</i> Chapter 4.8.1)
sertraline	Risk of hypotension, tachycardia, confusion, amnesia, aggression and serious liver and pancreatic disorders

See also *British National Formulary (BNF)*, Appendix 1.

## TACTICS TO AVOID THE RISK OF EXCESSIVE DRUG ABSORPTION

- 1 *The Easy Way Out (EWO)!* The simplest way of avoiding the risks of grapefruit juice is to tell all patients taking short-term or maintenance medication to avoid it. This is no great hardship, and a 'blunderbuss' approach makes life a little easier for the prescriber and the dispenser.

2 *A more subtle tactic.* Use your prescribing software to ‘flag up’ a warning message on the counterfoil of the prescription form, whenever one of the drugs listed in Table 2.1 is prescribed. This should always be accompanied by a strong verbal warning, since many patients don’t read counterfoil instructions, let alone those on the patient information leaflet (package insert).

Have no illusions – grapefruit juice is a major prescribing pitfall, especially in older patients and those with reduced kidney or liver function.

For the curious, the culprit in grapefruit juice has been identified as a furanocoumarol, also found in bitter oranges. This blocks the intestinal  $P_{450}$  enzyme irreversibly. However, the intestinal mucosa generates a fresh population of enzyme, usually within 24 hours.

***A footnote: cranberry juice***

Cranberry juice enhances the anticoagulant effect of warfarin, and other coumarins, in some patients.