



ACID TEST

Following his discovery that grapefruit juice can have a detrimental effect on the efficacy of certain medicines, **David Bailey**, University of Western Ontario, Canada, has found that the problem extends to other juices. He talks to **Nic Paton** about his findings and what can be done to prevent patients from taking a potentially fatal dosage.

Nearly 20 years, Dr David Bailey published his ground-breaking discovery that drinking grapefruit juice while taking medication can increase the absorption of certain drugs, so creating the potential for turning a normal dose of medicine into a much more dangerous, toxic overdose.

Bailey's identification of the 'grapefruit juice effect' has been linked to 50 medications, which all carry the risk of grapefruit-induced drug overdoses, and has led to many prescription drugs carrying labels for patients with the warning not to drink grapefruit juice or eat fresh grapefruit when taking the medicine.

Contributor profile



David Bailey is professor of medicine and physiology and pharmacology at the University of Western Ontario in Canada. He specialises in mechanistic and translational clinical pharmacological investigations related to drug interactions. Bailey's study 'Grapefruit juice - drug interactions' (*Lancet*. 1991;337:pp268-269) has been cited more than 300 times.

Not just grapefruit

In a blow to all those patients who still stubbornly prefer to wash down their drugs with juice rather than water, and in a finding of interest to pharmacists and medical professionals alike, Bailey has discovered that other common fruit juices can affect the efficacy of a number of other drugs.

In findings presented at the 236th annual meeting of the American Chemical Society of Philadelphia, Pennsylvania, in 2008, Bailey argued that other fruit juices can also affect the body's ability to absorb certain medications and therefore make the drugs less effective. His research suggested that these juices can reduce the effectiveness of certain drugs used to treat heart disease, cancer, organ-transplant rejection and infection.

'For some drugs, if you take your medication with grapefruit juice or other common juices, such as orange or apple, then the amount of drug that is absorbed would be decreased,' he says.

Trials

Bailey conducted a controlled human study of this type of drug-lowering interaction. In the trials, the volunteers, all healthy individuals, took fexofenadine, an antihistamine used to fight allergies, along with either a glass

DRUGS AFFECTED BY THE CONSUMPTION OF JUICES INCLUDE:

- Etoposide
- Atenolol
- Celiprolol
- Talinolol
- Ciprofloxacin
- Levofloxacin
- Itraconazole

of grapefruit juice, a glass of water with naringin (the flavonoid that gives the bitter taste to grapefruit juice) or plain water. Bailey found that the volunteers who drank the grapefruit juice absorbed only half the amount of fexofenadine, compared with those who drank plain water. The water with naringin was found to block one of the key drug transporters, called OATP1A2, which shuttled the drug from the small intestine into the bloodstream.

‘What worried us initially was, unlike with the original study where it was all about the possibility of an unintentional overdose toxicity, this time it was all about a potential loss of benefit of the drug,’ he says. ‘The drug has to be absorbed into the bloodstream to have its effect. If it stays in the gut it is almost like not having taken the drug. You have not only got inactivation of the drug, but also an inhibiting of the drug transport.’

By contrast, drugs with levels that were boosted in the presence of grapefruit juice appeared to block the important drug metabolising enzyme CYP3A4, which normally breaks down drugs. The research also discovered that orange and apple juices appeared to contain naringin-like substances that inhibit OATP1A2. The chemical in oranges appears to be one called hesperidin, while the chemical in apples has not yet been identified.

Among the drugs so far identified as being affected by the consumption of these juices are:

- anticancer agent Etoposide
- beta blockers Atenolol, Celiprolol and talinolol
- antibiotics, including Ciprofloxacin, Levofloxacin and Itraconazole.

It is expected that over time, as with the original grapefruit juice research, more drugs will be added to the list.

Bailey also identified that the reaction can occur with as little as 200ml of juice, or the equivalent of a single glass.

‘You don’t have to drink litres of the stuff to see a reduction of between 50-70%,’ he says. ‘This means you are only getting 30-50% of the drug absorbed because you are taking it within the juice.’

In practice, assuming a wider array of drugs are affected, this might mean a person taking an antidepressant may have too much or too little energy, someone on antibiotics might end up with diarrhoea, a heart patient might

not get the lowered blood pressure that a medication should deliver or suffer irregular heart rhythms, or it could alter the effectiveness of a woman’s hormone replacement-therapy medication.

Pharma delivery factor

Questions arise as to what this research means for the future delivery and delivery methods of pharmaceutical medication. One issue that Bailey is keen to address is how long the inhibiting effect lasts, as this will influence when a patient can drink fruit juice.

‘Clearly, the problems occur if you take the juice and the medication at the same time,’ he says. ‘But we have also been studying the time course and looking at, if you take your medication and have consumed juice two, four or ten hours beforehand, how long will you still have a problem for? If you have a drink two hours before, say, at breakfast, will it still affect your medication? Will you still be able to enjoy your juice as long as you space it out?’

Bailey recommends that people take their medication just with a glass of water on an empty stomach and then wait two to three hours before having a drink of juice, although that may be difficult in practise.

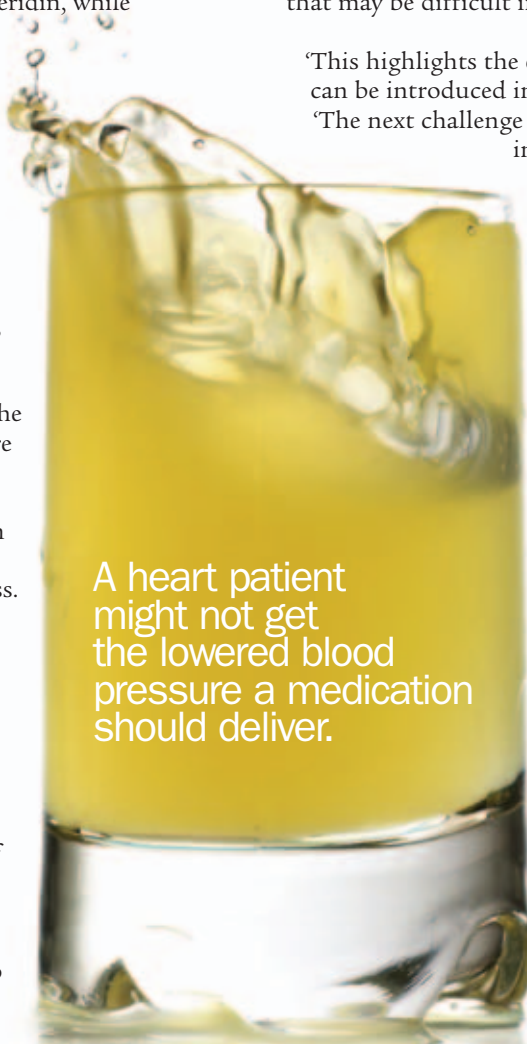
‘This highlights the extra levels of complexity that can be introduced into drug therapy,’ he explains.

‘The next challenge is to make sure this is translated into practice. But at least it is a relatively easy and straightforward concept to communicate to the general public.’

Communicator role

As much as the physician prescribing the drug and the willingness of the patient to take on board and understand health education messages, the key figure is the pharmacist. Pharmacists will have an important role in explaining to patients the requirement not to consume fruit or fruit juices with the medication, and they may well be able to learn lessons from the original grapefruit juice research.

‘Pharmacists will be the key link in the information chain when it comes to educating the public about this issue and encouraging them to change their ways,’ says Bailey. ‘In Canada, stickers on prescription vials have the warning, “do not consume grapefruit juice while taking this medication”. From the latest



A heart patient might not get the lowered blood pressure a medication should deliver.

research, this should be the sort of thing that should go on vials elsewhere, too.’

Rather than forcing patients to change their lifestyles and relying on them to remember such guidelines, the drug could be simply reformulated. However, Bailey is sceptical.

‘There does not seem to be an obvious way around it,’ he argues. ‘A sticker warning is the most straightforward approach. Trying to reformulate the drug would be very difficult and would add another layer of complexity. We do not have all the answers yet. But the best thing is that, because of the original research, people understand that this is a real issue. It has been accepted, and having that credibility factor is important.’

Getting the message across is important, as many nurses and doctors may still not be aware of the full consequences of drinking juice while taking medication (or simply need



THE ORIGINAL GRAPEFRUIT STUDY

Described by some observers as one of the ‘great moments in science’, Bailey’s 1991 study was the result of sheer chance. He and fellow researchers at the University of Western Ontario, Canada, were trying to find out if alcohol had any effect on the blood pressure drug felodipine, but wanted to keep the presence of the alcohol, which has a strong, burning taste, hidden from the volunteers.

The night before the study, Bailey discovered that the only thing that

covered the taste of the alcohol was grapefruit juice. Assuming the juice was inert as far as the study was concerned, it was used to mask the taste of alcohol. But the researchers immediately found something unexpected was happening: the drug levels in the blood of volunteers taking the grapefruit juice were three times higher than expected.

Bailey contacted the drug company to see if they had been sent wrongly labelled tablets, but they had not. He then conducted a mini-study

on himself. The first day he took felodipine with water and sent a blood sample off for analysis to see what levels of the drug he had in his blood. The second day, he took felodipine with grapefruit juice and, again, sent off a blood sample. Even before the results came back Bailey knew the answer. He experienced a headache, marked flushing of the skin and increased heart rate. The results showed that his plasma felodipine levels were five times higher with grapefruit juice than with water.

reminding) and many patients often fail to read the warning labels about drug-food interactions. Governments and health professionals will have to work in coordination to ensure the findings are clearly communicated and that the message gets through.

‘The only way to get around it is through education,’ says Bailey. ‘It is about translating the science in a way that helps the patient who is taking the medication, which often comes down to what the pharmacist tells them. Just putting a little sticker on the vial would be very helpful.’ **WPF**

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