

DRUG-FOOD INTERACTIONS

(1) FOOD AND MEDICINES*By Pamela Mason, PhD, MRPharmS*

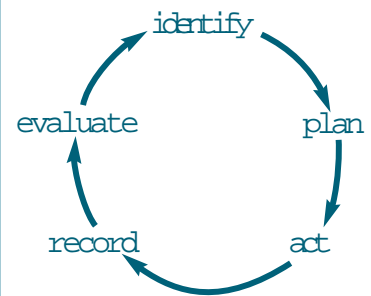
Some foods may affect the way in which the body handles medicines and therefore have the potential to either increase or decrease a drug's therapeutic or adverse effects. Conversely, medicines may affect the way the body handles food and can influence a patient's nutrition. This article is the first of two, focusing on both types of drug-food interaction



identify gaps in your knowledge

1. What are the two types of interaction between food and medicines?
2. Can you list three foods that commonly interact with drugs?
3. Do you feel confident to advise patients on drug-food interactions?

This article relates to the Royal Pharmaceutical Society's core competency of "drug-related interactions" (see "Medicines, ethics and practice — a guide for pharmacists", number 26, July 2002, pp105–6). You should consider how it will be of value to your practice.



When a food is delivered to the stomach, the stomach empties some of its contents within minutes. This is known as the adaptive phase of gastric emptying and the volume passed into the small intestine at this stage varies considerably. Most drugs are optimally absorbed in the small intestine and this initial gastric emptying provides the first opportunity for a drug taken with food to be absorbed, leading to the development of the first plasma drug peak. The height of this peak depends on the speed of gastrointestinal transit (the time taken for the food to pass through the body). A rapid transit decreases the peak and a slow transit increases the peak.

During the adaptive phase various hormones are released (eg, cholecystokinin), which lead to retention of material in the stomach. Fatty foods are the most potent inducers of these hormones. Although the total amount of drug absorbed may be unaffected, solid foods (particularly those rich in fat or dietary fibre) delay the entry of an orally administered drug into the duodenum, reducing the rate of absorption and hence the onset of therapeutic action. In addition, the presence of carbohydrate in the ileum can slow gastric emptying by altering gastrointestinal contraction patterns. Carbohydrate ingested with one meal can therefore influence gastric emptying at the next.

When medicines are taken with food, there is usually a second plasma drug peak. This corresponds to the delivery of the drug into the intestine with the food. The height and duration of this peak depend again on gastrointestinal transit time but also on the size and timing of the first peak in that current plasma levels of the drug will influence its further absorption (especially drugs absorbed by simple diffusion). The size of drug particles is also important. Particles up to 1.1mm in diameter are emptied into the small intestine with food, but larger particles are retained until gastric digestion is complete. The largest particles do not pass into the intestine until the stomach is empty so if there is insufficient time between meals for the stomach

to empty, some drugs are not absorbed until during the night. The risk of this can be minimised by taking the medicine on an empty stomach and avoiding eating between meals. There is some evidence that taking enteric-coated tablets with food severely delays absorption and again, the drug may only arrive in the intestine at night.

When drugs are taken with water alone, there is only one peak in plasma concentration. The rate of drug absorption depends on the dissolution rate, the speed of gastric emptying and gastrointestinal transit time. Rapid delivery from the stomach speeds absorption. However, if gastrointestinal transit is fast, the total amount absorbed will be reduced. Optimal plasma concentration could be achieved by taking the medicine with food.

It is difficult to be precise about the effects of food on drug absorption in individuals. Factors such as gastrointestinal transit time, sex, age, the presence of gastrointestinal disease, and for women, the stage of the menstrual cycle, can influence drug absorption and the effect of food on absorption. In general, however, the traditional recommendation to take medicines with a glass of water on an empty stomach will, in most cases, help to ensure optimal absorption. Water is the best drink to take because other drinks, such as milk, may prejudice the absorption of some medicines. The effect of caffeine-containing drinks, either hot or cold, (eg, coffee, tea, chocolate, cola) has not been well studied, but there is little evidence that such drinks influence drug absorption except in the case of theophylline (see below). It is preferable to take medicines with cool liquids so as to avoid heat labile drugs being destroyed. Fruit juices may decrease the effectiveness of acid labile drugs like penicillin. Tea decreases the absorption of iron.

When a fast therapeutic effect is required (eg, analgesia), it is best to take a medicine on an empty stomach. However, some drugs (eg, aspirin and other non-steroidal anti-inflammatory drugs) cause gastrointestinal irritation and food can be used to counteract this side effect. This can be a snack and need not be a full meal.

Delay in drug absorption is likely to be significant when therapeutic efficacy depends on the maintenance of constant blood levels of the drug. In such cases, the medicine should be taken at the same time in relation to food on each occasion. For example, taking one dose of an antibiotic half an hour before food, then the next dose

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with food could result in erratic absorption. On the other hand, meals can act as a reminder to take medication and, generally, people should not be dissuaded from taking their medicine because they have just eaten a meal even when the medicine should ideally be taken on an empty stomach.

The British National Formulary lists cautionary labels that cover drug administration in relation to food (eg, label 23, an hour before food or an empty stomach) and is the most convenient source of information for specific medicines. More detailed information can sometimes be found in data sheets or from medicines information centres.

CASE STUDY

Mrs Goddard brings her prescription to your pharmacy. She says she has heard that she should not drink grapefruit juice with her medicine and she asks you whether there are any other foods she should avoid. The prescription is as follows:

Propranolol 80mg *bd* x 60
Losartan 50mg *od* x 30
Warfarin 3mg *od* x 90
Phyllocontin Continus 225mg *bd* x 60

What are the specific effects of food on propranolol?

The liver metabolises most drugs to some extent, but propranolol is particularly susceptible to hepatic degradation. Food can increase blood flow to the liver and therefore the rate at which the drug passes through the liver. This results in a larger proportion of the drug passing intact into the systemic circulation.

However, for patients on maintenance doses this effect is not clinically significant. The lipophilicity of propranolol means that it is stored in adipose tissue (creating a reservoir), and this can decrease fluctuations in plasma levels. In addition, beta blockade lasts well beyond the four-hour plasma half-life. With a twice a day dosage, therefore, it does not usually matter whether propranolol is taken with or without food.

What are the specific effects of food on losartan?

It is well known that grapefruit juice increases plasma levels of drugs such as dihydropyridine calcium channel blockers and terfenadine because it inhibits CYP3A4 enzymes. CYP3A4 is found in the liver and expressed in the gut. Inhibition of CYP3A4 in the gut may lead to maximal absorption of a drug. However, recent research shows that grapefruit juice has another mode of action. The juice activates the efflux pump P-glycoprotein, which ejects drug molecules from the gut wall and back into the intestine. Studies have found that grapefruit juice reduces the absorption not only of losartan, but also of digoxin, fexofenadine, ciclosporin and vinblastine. On this basis, grapefruit juice could affect the action of many other drugs (eg, HIV protease inhibitors, immunosuppressants and anticancer agents) which are substrates for both CYP3A4 and P-glycoprotein.

If these findings are confirmed, patients who wish to drink grapefruit juice could avoid the counter absorptive effects of P-glycoprotein by drinking it about two hours before or after taking their medicine. However, as with all drug-food interactions, it is important not to make changes to the diet. In other words, patients should be advised not to start drinking grapefruit juice if taking these medicines, but not to stop if they are already drinking it, and to drink it at the same time in relation to administration of the medicine.

What are the specific effects of food on warfarin?

Warfarin has a narrow therapeutic margin, and pharmacists will be well aware that a number of drugs, if taken with warfarin, can disturb anticoagulant control. Certain types of food can also influence warfarin metabolism, by stimulating cytochrome P450 enzymes in the liver. Large amounts of green vegetables, such as broccoli, Brussels sprouts, spinach and cabbage, appear to reduce the anticoagulant effect of warfarin. These vegetables contain substances known as indoles, which stimulate drug-metabolising enzymes and increase the rate at which warfarin is metabolised and eliminated from the body.

Green vegetables also contain large amounts of vitamin K, which has a separate effect on warfarin. Anticoagulants compete

with vitamin K to decrease the production of blood-clotting factors. If the supply of vitamin K is boosted abnormally, the synthesis of blood-clotting factors is favoured and the effects of the anticoagulant are reduced.

There have been rare reports that large quantities of ice cream (greater than 1 litre a day) can reduce the effects of warfarin, and eating avocados can reduce the effects of warfarin.

Mrs Goddard tells you that her son is getting married in four weeks time. She is overweight and would like to lose a few pounds for the big day. She is thinking of adopting the Atkins diet.

What effect could a crash diet have on Mrs Goddard's drug therapy?

If Mrs Goddard loses weight rapidly (which she could do on any type of crash diet), this could lead to a change in drug distribution in the tissues. Loss of body fat may, in the short term, result in an increase in the plasma concentration of lipid-soluble drugs (in Mrs Goddard's case, propranolol) and increased therapeutic activity. When Mrs Goddard stops dieting it is likely that her weight will increase. Propranolol will be drawn preferentially into the adipose tissue and this could lead to a temporary reduction in the clinical effectiveness of the propranolol until her weight stabilises.

In addition, the risk of vitamin deficiency is increased with crash dieting. Most drugs undergo biotransformation in the liver before excretion and this involves a number of enzymes and co-factors, many of which are vitamin dependent. Vitamin deficiencies could reduce the activity of the drug-metabolising enzymes, leading to an increased risk of drug toxicity.

The Atkins diet is a high protein, high fat, low carbohydrate diet. Theophylline is extensively plasma protein bound so the ratio of protein to carbohydrate in the diet is important. A high protein diet increases the metabolism of theophylline and may reduce its effectiveness. If, on the other hand, carbohydrate is increased at the expense of protein, theophylline metabolism proceeds at a slower rate and the risk of theophylline toxicity is increased. If Mrs Goddard adopts the Atkins diet, the effectiveness of theophylline may be reduced.

Everybody should be discouraged from going on crash diets, but this is particularly important for a patient like Mrs Goddard who is on long-term drug therapy. If weight loss is necessary, it should be achieved gradually. Pharmacists should be alert for any adverse drug effects or worsening of symptom control in patients who have lost or gained a great deal of weight over a short period of time.

What overall advice should Mrs Goddard be given in relation to food and drink?

The most important thing for Mrs Goddard is that she takes her medicines at the same time each day in relation to meals and snacks. This will help to reduce the risk of erratic absorption. If Mrs Goddard enjoys a glass of grapefruit juice, she could drink it two hours before or after taking her losartan. It would be worth reminding her not to start drinking grapefruit juice if it is not currently part of her diet.

In relation to warfarin and theophylline, the main aim is not to make significant changes to the diet (eg, suddenly increasing protein intake). To achieve a healthy diet, green vegetable consumption is encouraged, but it is important not to make sudden, massive changes in intake. This might be prompted by particular vegetables coming into season, but these days, when dark green vegetables are available all year round, a regular, balanced intake should be achievable.

Mrs Goddard's caffeine intake should be kept stable. This is because caffeine and theophylline are metabolised along similar pathways, and the therapeutic margin for theophylline is narrow. Increased coffee intake reduces theophylline metabolism and may increase blood levels, while reducing coffee intake has the opposite effect and may result in the need to increase the dose of theophylline.

Mrs Goddard should be advised to drink alcohol only in moderation at her son's wedding, because drinking large amounts can affect warfarin control. Patients taking propranolol should also drink in moderation.

In the interest of achieving a balanced diet, Mrs Goddard should not avoid any foods completely. A summary of the interactions cov-

ered in this case study and a few other drug-food interactions are listed in the panel below.

Correction

The statement "eating avocados can enhance the effects of warfarin" is not correct. The true position is as stated in the Panel on p573: "The effects of anticoagulants may be reduced by avocado but there is insufficient evidence at present to advise avoiding it."

action : practice points

1. Revise your knowledge of the digestive system and the processes involved in digestion (eg, visit www.cybemorth.com/anatomy/digestive.htm)
2. How long after finishing a course of metronidazole should a person wait before he or she can drink alcohol? If you do not know for sure, research the answer.
3. Select a patient group and find out how aware people are about the effect of foods on their medicines. For example, you could target patients on warfarin: although eating green vegetables should not be discouraged, are most of these people aware that they should not make huge changes to the quantity of green vegetables that they eat?

evaluate

How could your learning have been more effective?
What will you do now and how will this be achieved?

DRUG-FOOD INTERACTIONS

This panel lists some common drug-food interactions. Further interactions can be found in a leaflet produced by the United States Food and Drug Administration and the National Consumers League (www.fda.gov/cder/consumerinfo/druginteractions.htm)

DRUGS ACTING ON THE GASTROINTESTINAL SYSTEM

- 1 *Tripotassium dicitratobismuthate (bismuth chelate)*: Large volumes of milk can reduce ulcer healing properties of bismuth chelate (small amounts in tea and coffee do not matter)

DRUGS ACTING ON THE CARDIOVASCULAR SYSTEM

- 1 *Calcium-channel blockers*: Grapefruit juice increases serum levels of nifedipine and possibly other dihydropyridines and should be avoided
- 1 *Anticoagulants*: The effects of anticoagulants may be reduced by avocado but there is insufficient evidence at present to advise avoiding it. The effects of anticoagulants can also be reduced or even abolished by large amounts (greater than 500g daily) of green vegetables (eg, spinach, sprouts, broccoli) and excessive consumption should be avoided. It has been found that large quantities (>1 litre at once) of ice cream antagonise the effect of warfarin. The effects of warfarin may also be reduced by large amounts of soya bean products
- 1 *ACE inhibitors*: Eating large amounts of potassium-rich foods (eg, bananas) should be avoided because of the risk of hyperkalaemia

DRUGS ACTING ON THE RESPIRATORY SYSTEM

- 1 *Theophylline*: High protein diets may reduce the bioavailability of theophylline and high carbohydrate diets increase it. Major changes to the diet should be avoided. Caffeine increases the risk of insomnia and cardiac arrhythmias in susceptible individuals and excessive intake (eg, more than five cups of coffee a day) should be avoided.
- 1 *Terfenadine*: Avoid grapefruit juice

DRUGS ACTING ON THE CENTRAL NERVOUS SYSTEM

- 1 *Tricyclic antidepressants*: High fibre diets may reduce serum

levels of of tricyclic antidepressants and prevent relief of depression. There is no need to eat a diet low in fibre, but check the diet if drug fails to work.

- 1 *Lithium*: Dietary salt restriction can increase serum lithium to toxic levels. Increased intake of salt or use of sodium containing medicines can prevent establishment or maintenance of adequate serum lithium levels. Patients stabilised on lithium should not alter sodium intake
- 1 *Monoamine oxidase inhibitors*: Tyramine-containing food and drink (eg, mature cheeses, avocados, soy sauce) can precipitate a hypertensive crisis and must be avoided
- 1 *Levodopa*: High protein intake reduces the effects of levodopa. Patients stabilised on levodopa should not make large changes to the diet

DRUGS USED IN THE TREATMENT OF INFECTIONS

- 1 *Tetracyclines*: The absorption of tetracyclines is reduced by milk and dairy foods (doxycycline and minocycline are not affected). Doses should be separated from intake of milk and dairy foods by at least two hours
- 1 *4-quinolones*: Absorption of ciprofloxacin and norfloxacin (but not ofloxacin) is reduced by milk and dairy food, and doses of these drugs should be separated from milk and dairy foods by at least two hours
- 1 *Isoniazid*: Histamine-containing foods (eg, cheese, fish) may induce a flushing reaction with headache, breathing difficulty, nausea and tachycardia. No dietary restriction necessary, but the patient's diet should be looked at if these reactions occur
- 1 *HIV-1 protease inhibitors*: Fat reduces absorption of protease inhibitors and grapefruit juice improves absorption. These drugs should be taken two hours apart from meals or grapefruit juice

DRUGS USED FOR IMMUNOSUPPRESSION

- 1 *Cyclosporin*: Grapefruit juice may reduce absorption and should be avoided or not be drunk within two hours of a dose
- 1 *Anticancer agents*: Grapefruit juice may reduce absorption of these some anticancer agents, so should be avoided or not be drunk within two hours of a dose