Meals and medicines

Andrew McLachlan and Iqbal Ramzan, Faculty of Pharmacy, University of Sydney, NSW

Summary

Food and its constituents may have a significant effect on both the rate and extent of absorption of drugs after oral administration. Understanding the effect of meals on medicines enables health professionals to advise patients about taking medicines with or without food. Co-administration of drugs with food generally delays drug absorption. However, meals may have a variable effect on the extent of absorption – depending on the characteristics of the meal, the drug and its formulation. Some drugs have strict guidelines about when they should be taken in relation to meals. Generally, patients should be advised to take their medicines consistently at the same time with respect to meals.

Key words: bioavailability, drug interactions, food.

(Aust Prescr 2006;29:40–2)

Introduction

Understanding the possible clinical implications of taking medicines with or without a meal is important for achieving quality use of medicines. Although the effect of food is not clinically important for many drugs, there are food–drug interactions which may have adverse consequences. Often these interactions can be avoided by advising the patient to take their medicines at the same time with respect to meals.

The effect of food on absorption

The formulation of a drug influences its absorption. Food can affect both the rate and extent of absorption (Table 1).

Rate of absorption

Meals slow down gastric emptying and this can delay drug absorption. The composition of the meal influences the rate of gastric emptying – high fat meals lead to delayed gastric emptying. A delay in the drug reaching the small intestine can delay its subsequent absorption into the systemic circulation. Based on these observations, oral administration of a medicine under fasting conditions is often recommended when rapid absorption (and hence rapid onset of therapeutic effect) is needed. For most medicines, especially those used for chronic conditions, a delay in the onset of absorption is of no clinical consequence as long as the amount of drug absorbed is unaffected.

Extent of absorption

Food has the potential to either increase or decrease the extent of drug absorption. Understanding food–drug interaction mechanisms enables the clinician to provide appropriate advice to patients about taking medicines with respect to the timing and composition of meals.

The effect of food depends on the physicochemical and pharmacokinetic characteristics of the drugs.[1] The clinical significance of the effect will in turn depend on the pharmacodynamic characteristics of the drug. For example, the poorly water soluble antiretroviral drug saquinavir should be taken with food to allow bile enhancement of its dissolution which then facilitates absorption. The extent of absorption is more than doubled by taking saquinavir after a full cooked breakfast. Taking saquinavir on an empty stomach reduces its bioavailability and could lead to therapeutic failure.[1]

Delayed gastric emptying after a meal and the associated gastric acid secretions can reduce the bioavailability of some medicines that are acid labile. The constituents of a meal may also specifically interact with drugs (Table 2). Calcium and other cations in food can form insoluble chelates with some medicines preventing their optimal absorption. Bisphosphonates are therefore recommended to be taken with plain water to prevent the formation of chelates which significantly reduce bioavailability.

Grapefruit juice: an important example

Co-ingestion of grapefruit juice and certain drugs (Table 3) significantly increases their bioavailability because the constituents of the juice inhibit pre-systemic drug metabolism or transport. This increase in bioavailability can lead to excessive beneficial or adverse effects.[2] The effects of grapefruit juice are complex and have been widely studied.[3,4]

A single glass of grapefruit juice is enough to increase the bioavailability of some drugs. If the juice is drunk over several days the effects are long-lasting[3,4], so simply separating the dose of medicine and the ingestion of grapefruit juice does not prevent the interaction. For this reason grapefruit juice ingestion should be avoided completely with certain drugs, for example cyclosporin.

Could grapefruit juice be routinely used to enhance the bioavailability of some medicines? The answer would appear to be no because the effect of grapefruit juice on drug absorption is highly variable. It depends on the constituents of the juice, how it is prepared and varies with brands and batches.

Table 1

Mechanisms of food–drug interactions [1]

Mechanism	Medicines or class	Implication	Actions *
Poor acid stability	azithromycin† ampicillin† erythromycin (some salts)† isoniazid phenoxymethylpenicillin	Exposure to acid and prolonged gastric residence leads to chemical degradation and reduced bioavailability with risk of therapeutic failure	Take on an empty stomach († or at a consistent time with respect to meals)
Chelation	bisphosphonates ciprofloxacin norfloxacin penicillamine	Reduced therapeutic effect	Take on an empty stomach († or at a consistent time with respect to meals)
Acid dependency	amprenavir itraconazole (capsules) ketoconazole	Reliable absorption depends on acid environment	Take with meals or at a consistent time with respect to meals
Bile acid or fat enhanced drug dissolution	acitretin carbamazepine griseofulvin isotretinoin halofantrine mefloquine saquinavir tacrolimus	Enhanced bioavailability	Take with meals or at a consistent time with respect to meals
Physical binding/adsorption	digoxin	Digoxin may bind to fibre reducing its bioavailability	Avoid concurrent ingestion with fibre or take digoxin at consistent time with respect to meals
Reduced gastric emptying	most medicines	Reduced rate of absorption	Take at a consistent time with respect to meals

* Note: Taking a medicine with a meal implies taking the dose within 30 minutes of a meal. Taking a medicine on an empty stomach implies taking the dose one hour before or two hours after a meal.

Table 2

The effect of specific dietary components on selected drugs [1]

Specific foods	Medicine (class)	Advice on meals and implications
Vitamin K rich foods	warfarin	Dietary intake of vitamin K rich foods should be consistent to avoid fluctuation in INR. Abstinence is not required.
Potassium rich foods and supplements	ACE inhibitors, potassium sparing diuretics, and angiotensin receptor antagonists	Foods and accompaniments high in potassium should be ingested in moderation to avoid the risk of hyperkalaemia
High protein meal	levodopa	Reduce the cerebral uptake (not bioavailability) of levodopa and potentially reduce clinical efficacy
Tyramine rich foods	monoamine oxidase inhibitors	Significant risk of hypertensive crisis
Calcium rich foods	tetracycline quinolones	Co-administration of calcium rich foods and supplements results in chelation and reduced drug absorption with a risk of therapeutic failure

Table 3

Drugs affected by oral co-ingestion of grapefruit juice [3,4]

Advice to patients	Drug
Avoid co-ingestion of grapefruit juice due to risk of unwanted effects	amiodarone atorvastatin cyclosporin diazepam felodipine midazolam nifedipine saquinavir sildenafil simvastatin verapamil
Co-ingestion of grapefruit juice may be acceptable with appropriate monitoring and awareness	amlodipine diltiazem ethinyloestradiol pravastatin prednisolone/prednisone theophylline

Grapefruit juice is not 'pharmaceutical grade' or consistently of the same 'quality', so co-administration with a drug would lead to a variable response.

Studying the effect of food

The product information approved by the Therapeutic Goods Administration is the main source of information about the possible effects of food on drug absorption. This information is generally derived from a 'food effect study' that is conducted during drug development. Typically, this involves a randomised cross-over single dose pharmacokinetic study in healthy people. They take the drug of interest after an overnight fast and also after a standard high fat breakfast. This design is meant to examine the effect of food under 'extreme' conditions. Unfortunately, a volunteer eating a high fat meal does not necessarily reflect the circumstances of the patients who will take the drug. Dosing recommendations with respect to food derived from these studies may therefore not provide the best guide to the actual impact of food on drug absorption.

Taking medicines with meals to help adherence, tolerability and efficacy

Prescribing a drug regimen that fits in with the patient's daily routine (which is usually centred around mealtimes) can enhance the patient's adherence to treatment. This leads to the general recommendation that patients should take their medicines at prescribed and consistent times relative to their meals. This is despite the fact that the absorption of some medicines may be significantly reduced when taken with food, for example atorvastatin and thyroxine. Patients should also be informed if particular foods can interfere with their treatment (Table 2).

Some medicines (for example non-steroidal anti-inflammatory drugs and metformin) are taken with food to minimise the risk of gastrointestinal adverse effects. Repaglinide and the sulfonylureas should be taken before a meal to avoid the risk of significant hypoglycaemia. In the case of repaglinide, if a meal is skipped then the drug dose should also be skipped. Similarly, taking acarbose with meals is essential to ensure its maximum efficacy in delaying the intestinal absorption of carbohydrates.

Conclusion

Meals may have variable and often unpredictable effects on drugs via a range of mechanisms. By understanding and appreciating the clinical consequences of these effects health professionals can provide advice about the appropriateness of ingesting medicines with respect to the times and the composition of meals. The provision of timely and appropriate advice about the possible effects of meals on medicines and the importance (or lack) of the timing of meals and medicines is an important issue impacting on the quality use of medicines.

References

1. Schmidt LE, Dalhoff K. Food-drug interactions. Drugs 2002;62:1481-1502.
2. McNeece J. Grapefruit juice interactions. Aust Prescr 2002;25:37.
3. Bailey DG, Malcolm J, Arnold O, Spence JD. Grapefruit juice-drug interactions. Brit J Clin Pharmacol 1998;46:101-10.
4. Dahan A, Altman H. Food-drug interaction: grapefruit juice augments drug bioavailability - mechanism, extent and relevance. Eur J Clin Nutr 2004;58:1-9.

Further reading

Birkett DJ. Pharmacokinetics made easy. 2nd ed. Sydney: McGraw-Hill; 2002.

Coxeter PD, McLachlan AJ, Duke CC, Roufogalis BD. Herb-drug interactions: an evidence based approach. Curr Med Chem 2004;11:1513-25.

Fugh-Berman A. Herb-drug interactions. Lancet 2000;355:134-8.

Associate Professor McLachlan and Associate Professor Ramzan have acted as consultants to the pharmaceutical industry and are members of the Pharmaceutical Subcommittee of the Australian Drug Evaluation Committee (ADEC).

Self-test questions

The following statements are either true or false (answers on page 55)

3. Taking bisphosponates with milk increases their bioavailability.
4. The bioavailability of some drugs is increased by a high fat meal.