Food-drug interactions: Do they really matter?

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Educational aims

- To have a better understanding of the types of interaction occur between food and medicines
- To be better informed on the advice that patients should be given on drug-food interactions

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In pharmacists' daily practice, particularly when advising patients regarding their dosage regimen, they are often faced with the recurring question "do I need to take this after a meal?" Sometimes it makes one wonder whether this is a true concern or whether it is just an excuse to eat! The truth, however, is that interactions between food and medicines can have a significant influence on the adverse effect profiles of many drugs and on the therapeutic success of the drug being administered.

A food-drug interaction may be defined as the alteration of absorption, metabolism, elimination or effect of a drug by a food component.[1]

Now, a number of questions follow – how knowledgeable are healthcare professionals about this subject? How willing are they to provide the correct information to the patient by looking it up on a reference book or on the patient's insert? Do they have the necessary tools at hand? Do they have the time?

Regardless of the response to these questions healthcare professionals are duty bound to provide this information in a correct manner to the patient and in failing to do so they might compromise patient care. Severe adverse reactions, therapeutic failures and fatalities have been reported following food-drug interactions.[2]

Foods – general

The first occasion for a food-drug interaction to occur is during the absorption phase of the drug. Most drugs are optimally absorbed in the small intestine and food ingestion can either reduce or increase the rate or extent of absorption.[3,4]

With some drugs the presence of increased amounts of stomach acid results in the destruction of acid-labile drugs.[3,5]. In other cases food components such as calcium or iron may chelate some drugs reducing their absorption. Delayed absorption does not necessarily reduce the total overall exposure to the drugs and the area under the curve (AUC) may be equivalent regardless of how the drug is taken.[5] On the other hand some medicines should be taken after meals since their bioavailability is enhanced by food.[1] Table 1 summarizes some of these interactions.

Alcohol

The two main types of interactions, which can occur following concurrent alcohol and medicine ingestion, are (i) CNS depression and (ii) the flushing reaction.[6] The effects of drugs that have CNS depressant activity are enhanced by consumption of alcohol, thus impairing driving ability and other skills. This interaction involves drugs such as amphetamines, analgesics, antiepileptics, antihistamines, antipsychotics, appetite suppressants, benzodiazepines, isoniazid, lithium, maproteline, metoclopramide, mianserin, selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants.[6]

The flushing reaction also known as a disulfiram reaction occurs between alcohol and some drugs, chemicals and certain fungi, and although unpleasant and possibly frightening it is rarely dangerous.[5,6] This reaction is expected with disulfiram since it blocks the metabolism of alcohol and leads to an accumulation of acetaldehyde in the blood stream resulting in flushing, fullness of the face and neck, tachycardias, breathlessness, giddiness, hypotension, nausea and vomiting.[5,6,7] The reaction can occur with 10 minutes of alcohol ingestion and may last several hours.[7] Drugs reported to provoke a similar reaction include azole antifungals, cephalosporins, furazolidone, griseofulvin, metronidazole and topical tacrolimus and pimecrolimus.[6]

Alcohol should also be avoided in

Table 1. Before food, with food or after food?

Recommendation	*Drugs*	*Reason*
Take with a high fat meals	• Griseofulvin • Albendazole	Increased absorption
With food	• Acitretin • Carbamazepine • Fenofirate • Isotretinoin • Itraconazole capsules • Ketoconazole • Labetalol • Lopinavir • Mebendazole • Tamsulosin • Tenofovir	Food enhances bioavailability
	• NSAIDs + Aspirin • Co-amoxiclav	To minimise gastrointestinal adverse effects
1 hour before food or 2 hours after	• Azithromycin capsules • Indinavir • Itraconazole solution • Lansoprazole • Penicillins • Quinolones • Saquinavir • Tetracyclines	Food reduces bioavailability either because drugs are acid-labile or via the formation of complexes with the drug
30 minutes before food	• Didanosine • Perindopril • Rifampicin	
	• Alendronate • Risedronate	Specifically 30 minutes before the first food of the day
2 hours after eating	• Strontium	Reduced bioavailability

patients on concurrent hepatotoxic medications such as paracetamol, methotrexate, leflunamide, and phenytoin.[6,8]

Grapefruit and grapefruit juice

Grapefruit and grapefruit juice alter the pharmacokinetics of several drugs such as statins, calcium channel blockers, antibiotics and others. This was, as often is the case, discovered accidentally in a study investigating alcohol-drug interactions where grapefruit juice was utilised to mask the taste of the alcohol being studied.[9] The major mechanism in the induction of grapefruit-drug interactions seems to be the ability of grapefruit to inhibit intestinal CYP3A4, thus reducing 'first-pass' metabolism leaving a higher concentration of drug circulating in the body.[2,5,9] The concern is that concomitant administration of a single serving of grapefruit or its products with certain drugs may cause toxic effects based on increased exposure.[9] For those patients who are unwilling to terminate their consumption of this product, alternative drugs within the same class that exhibit a weak or no interaction should be prescribed. Table 2 summarizes the most significant drug-grapefruit interactions.

Cranberry juice

Cranberry juice has gained a lot of popularity in recent years because of claims that it reduces the risk of urinary tract infections[10] and because of its antioxidant potential. However, the current recommendation of the CSM (Committee on Safety of Medicines)/MHRA (Medicines and Healthcare products Regulatory Agency) in the UK is that patients taking warfarin should limit or avoid completely drinking cranberry juice.[2]. This measure was taken following reports that the anticoagulant effects of warfarin were increased in patients drinking cranberry juice. One patient had a very marked increase and died from a haemorrhage while a further patient had a reduction in his INR (International Normalized Ratio).[2,11]

Milk and dairy products

The absorption of most tetracyclines is markedly reduced by milk and other dairy products. Reduction is reported at up to 65%.[5] Doxycyline and minocycline are less affected by this food group although a reduced absorption of 25-30% is reported.[2] Dairy products also reduce the bioavailability of ciprofloxacin and norfloxacin.[5] As a consequence, it is usual to recommend that tetracyclines and quinolones are taken one hour before food or 2 hours after food to avoid an interaction with all forms of dairy calcium.[2]

In the case of strontium, the manufacturer remarks that food, milk and dairy products reduce the bioavailability of strontium by 60 to 70% when compared to bioavailability following administration 3 hours after a meal. For this reason recommendations state that strontium should be taken at bedtime at least 2 hours after eating.[2,12]

Caffeine

Caffeine is a methylxanthine derivative that is contained in tea, coffee, chocolate, and beverages and in compound analgesic preparations. Caffeine is a proven ergogenic aid, increasing athletic performance, endurance, and mental chronometry even at very low doses.[13] As a consequence of this it is likely that caffeine-containing products will reduce the efficacy of hypnotics and increase the risk of insomnia. Patients on antiarrythmics should also avoid excessive caffeine because of the risk of tachycardias.

Theophylline, which is chemically related to caffeine and licensed for the prophylaxis and treatment of reversible bronchospasm associated with asthma and chronic obstructive pulmonary disease, is a xanthine-derivative. Thus the concurrent consumption of other xanthine-containing products is contraindicated.[14]

With high doses caffeine also reduced the seizure threshold and produced a significant reduction in the anticonvulsant effects of carbamazepine, phenobarbitone, phenytoin, and valproate in mice.[15] This interaction was pharmacodynamic in nature since caffeine did not affect the plasma concentrations of these anti-epileptics. In case of newer antiepileptics, both acute and chronic caffeine decreased the protective potential of gabapentin and topiramate but not that of lamotrigine and tiagabine.[17] Regardless of this however none of the manufacturing companies advise against the consumption of such products.[16,17,18,19,20,21,22]

It is advisable to avoid caffeine-containing products with other stimulant products such as ginseng, guarana, pseudoephedrine and ephedra (available in some slimming preparations). Fatalities have been reported with concomitant ephedra and caffeine use.[23]

Protein

Protein content in the diet may cause fluctuations in the response of parkinsonian patients being treated with levodopa. This is thought to be due to a reduction in the efficacy of levodopa secondary to the action of the amino acid methionine and a reduction in the blood levels of levodopa as a result of the amino acid tryptophan. Spreading out the intake of proteins and restricting daily allowance of protein to 800mg/kg body weight is reported to reduce this interaction.[2]

Tyramine – rich foods

Perhaps the most feared food-drug interaction is that between monoamine oxidase inhibitors (MAOIs) and the amino acid tyramine.[2,5] Tyramine is indirectly sympathomimetic and when its metabolism is suppressed, as it is by MAOIs, it can cause a significant release of norepinephrine, resulting in markedly increased blood pressure, cardiac arrhythmias, hyperthermia and cerebral hemorrhage. Fatalities have been reported[5]. As little as 6mg of tyramine can raise the blood pressure and 10 to 25mg of tyramine would be expected to cause a serious hypertensive reaction. Tyramine is found in foods such as cheeses, salami, sausages, smoked meats, yeast extracts, pickled foods, chocolate and drinks such as beers and wine. Since the tyramine levels vary so much it is impossible to guess the amount of tyramine present in any food and drinks.[2]

Table 2. Interactions with grapefruit and grapefruit products[2,9]

Interacting drug *(oral form only)*	***Expected effect of interaction***	***Patient advice***
Amiodarone	Increased peak serum level by 84% and increased AUC of amiodarone by 50%. Reduced effect of amiodarone on the PR and QTc intervals.	It is prudent to suggest to patients that they avoid grapefruit juice.
Calcium Channel blockers	The significant increase in the bioavailability of felodipine may alter their haemodynamic effects. The bioavailability of nifedipine and nimodipine is also increased without altering the haemodynamic effect. The bioavailability of amlodipine, diltiazem and verapamil is only minimally affected although with verapamil some ECG changes were seen.	The manufacturers of these products contraindicate the intake of grapefruit and its products, although this interaction is most significant in patients receiving felodipine.
Carbamazepine	Possible carbamazepine toxicity	Grapefruit or grapefruit juice should be avoided but if its consumption is desirable, carbamazepine levels should be monitored.
Cyclosporin	Trough and peak serum levels and bioavailability of cyclosporin is increased.	Concurrent use should be avoided.
Pimozide	Raised pimozide levels may lead to potentially fatal torsades de pointes arrhythmias.	Concurrent use is contraindicated.
Sildenafil, Tadalafil and Vardenafil	Grapefruit juice can increase the area under curve (AUC) of sildenafil by 23%. Although this is unlikely to be clinically significant this combination is best avoided because concurrent use results in an increased variability in sildenafil pharmacokinetics. Products within the same class are likely to interact similarly.	Avoid concurrent use of grapefruit and grapefruit juice.
Simvastatin and Lovastatin	Plasma levels of lovastatin and simvastatin can increase by upto 12-fold and 9-fold respectively if given with grapefruit juice, increasing the risk of muscle damage and possible development of rhabdomyolysis.	Even small quantities of grapefruit and its products can cause a signification interaction and thus concomitant use should be avoided.
Sirolimus	Grapefruit juice may raise sirolimus serum levels.	Although the extent of this interaction is unknown the manufacturer suggest avoidance of this product.
Tacrolimus	Grapefruit juice can markedly increase serum levels of tacrolimus by up to 400%	Combination should be avoided if consumption is desirable close monitoring is recommended.

A milder form of this reaction has also been observed with moclobemide, selegiline and large quantities of tyramine rich foods (e.g. 300g Gorgonzola® cheese).[2]

Others

The effects of warfarin can be antagonized by vitamin K, which is found in large amounts in green vegetables such as spinach, broccoli, cabbage and green tea. Patients should be advised to avoid dramatic dietary alterations. Care should also be given to patients starting new vitamin supplements.[2] Other foods such as garlic, mango, avocado, soybean products and herbs are know to interact with warfarin and patients should be referred to their anticoagulant book for more information.[2,4,23]

Conclusion

This review has highlighted the outcome of some common food-drug interactions. Needless to say it is quite impossible for a pharmacist to remember all the known clinically important reactions, which is why there are suitable reference publications to refer to such as the British National Formulary, Stockley's Drug Interactions and specific product characteristics available on www.medicines.org.uk.

Pharmacists should not fear opening a book or a package insert in front of a patient in order to guide them accordingly. Priority should be given to patients on drugs, which have a narrow therapeutic index, such as warfarin, and to elderly patients who are most at risk due to polypharmacy, renal and hepatic impairment.

Multiple choice questions

A correct response of 80% and over will entitle MCPP members to 1 credit towards their annual continuous education requirement. Answers may be sent by email to: president@mcppnet.org by 30 September 2009.

1. Patients on oral hypoglycaemics should avoid excessive amounts of:
- ☐ a. Protein rich foods
- ☐ b. Alcohol
- ☐ c. Vegetables
- ☐ d. Black coffee with artificial sweeteners

2. Drugs which are acid-labile like penicillin have their efficacy reduced by:
- ☐ a. Water
- ☐ b. Orange juice
- ☐ c. Black Coffee
- ☐ d. Alcohol

3. Iron supplements has its absorption reduced by:
- ☐ a. Tea
- ☐ b. Water
- ☐ c. Orange Juice
- ☐ d. Black coffee

4. Patients on ACE inhibitors should avoid large amounts of salt-substitutes avoid the risk of:
- ☐ a. Constipation
- ☐ b. Hypotension
- ☐ c. Hypertensive Crisis
- ☐ d. Hyperkalaemia

5. How long after finishing a course of metronidazole should a person wait before he or she can drink alcohol?
- ☐ a. 12 hours
- ☐ b. 24 hours
- ☐ c. 48 hours
- ☐ d. 1 week

6. Excessive consumptions of alcohol may increase the risk of gastrointestinal haemorrhage in patients taking:
- ☐ a. NSAIDs
- ☐ b. Opioid analgesics
- ☐ c. Benzodiazepines
- ☐ d. Ginseng

7. Alcohol may cause facial flushing or skin erythema in patients using:
- ☐ a. Topical corticosteroids
- ☐ b. Topical NSAIDs
- ☐ c. Topical antihistamines
- ☐ d. Topical tacrolimus

8. When taken with grapefruit juice the following drug can cause severe rhabdomyolysis:
- ☐ a. Simvastatin
- ☐ b. Fluvastatin
- ☐ c. Atorvastatin
- ☐ d. Rosuvastatin

9. High doses of omega-3 marine triglycerides (4 capsules) increase bleeding time in patients on:
- ☐ a. Aspirin
- ☐ b. Warfarin
- ☐ c. Ticlopidine
- ☐ d. Clopidogrel

10. Food reduces the absorption of:
- ☐ a. Isotretinoin
- ☐ b. Azithromycin suspension
- ☐ c. Azithromycin capsules
- ☐ d. Ketoconazole

Practice points

- It is the duty of healthcare professionals to educate patients on the possibility of interactions between their medications and their diet.
- Patients require correct administration instructions so as to get the maximum benefit from their medicinal treatment and to avoid adverse reactions.
- Patients should be given clear information on the consequences of an alcohol-drug interaction as this can prevent severe outcomes.
- Patients buying vitamins and herbal medicines should always be asked for a medication history.
- If one knows that a patient is unlikely to stick to the dietary advice recommended with his/her medication than it would be advisable for the pharmacist to suggest an alternative.

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