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Food-Drug Interactions

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Contents

Abstract

Interactions between food and drugs may inadvertently reduce or increase the drug effect. The majority of clinically relevant food-drug interactions are caused by food-induced changes in the bioavailability of the drug. Since the bioavailability and clinical effect of most drugs are correlated, the bioavailability is an important pharmacokinetic effect parameter. However, in order to evaluate the clinical relevance of a food-drug interaction, the impact of food intake on the clinical effect of the drug has to be quantified as well. As a result of quality review in healthcare systems, healthcare providers are increasingly required to develop methods for identifying and preventing adverse food-drug interactions. In this review of original literature, we have tried to provide both pharmacokinetic and clinical effect parameters of clinically relevant food-drug interactions.

The most important interactions are those associated with a high risk of treatment failure arising from a significantly reduced bioavailability in the fed state. Such interactions are frequently caused by chelation with components in food (as occurs with alendronic acid, clodronic acid, didanosine, etidronic acid, penicillamine and tetracycline) or dairy products (ciprofloxacin and norfloxacin), or by other direct interactions between the drug and certain food components (avitriptan, indinavir, itraconazole solution, levodopa, melphalan, mercaptopurine and perindopril). In addition, the physiological response to food intake, in particular gastric acid secretion, may reduce the bioavailability of certain drugs (ampicillin, azithromycin capsules, didanosine, erythromycin stearate or enteric coated, and isoniazid). For other drugs, concomitant food intake may result in an increase in drug bioavailability either because of a food-induced increase in drug solubility (albendazole, atovaquone, griseofulvin, isotretinoin, lovastatin, mefloquine, saquinavir and tacrolimus) or because of the secretion of gastric acid (itraconazole capsules) or bile (griseofulvin and halofantrine) in response to food intake. For most drugs, such an increase results in a desired increase in drug effect, but in others it may result in serious toxicity (halofantrine).

Interactions between food and drugs can unintentionally reduce or increase the effect of the drug, resulting in therapeutic failure or increased toxicity. This may adversely affect patient care, contribute to morbidity and prolong treatment time or hospitalisation. Even though the extent of the problem is unknown, there is a need for strategies to identify and prevent the development of food-drug interactions.[1]

This review of original literature describes clinically relevant food-drug interactions. In the text, the drug groups are listed in accordance with the Anatomical Therapeutic Chemical (ATC) classification but, in the table, drugs with evidence of food-drug interactions are listed alphabetically (table I). For each drug, a dietary recommendation is given along with information on the proposed mechanism, consequences and qualifications of the interaction. Based on considerations of the potential severity of the interaction combined with the expected incidence, the table provides the authors' estimate of the clinical relevance of the interaction. In addition, the new Scottish Intercollegiate Guidelines Network (SIGN) system has been used to grade the scientific evidence.[2] Drugs such as peristaltic agents that require ingestion with a specific relation to meals because of their mode of action are not included in the review, nor are interactions with alcohol.

1. Mechanisms

Food-drug interactions can be divided into pharmacokinetic and pharmacodynamic interactions. Pharmacokinetic interactions (whereby food affects the absorption, distribution, metabolism or elimination of a drug) are by far the most common.

Table I. Guiding recommendations for administration of drugs with potential food-drug interactions. Level and grade of scientific evidence are determined using the SIGN guideline system[2]

Drug or class	Clinical relevance	Dietary recommendation	Proposed mechanism of interaction	Consequences and qualifications of interaction	Level[a]/grade[b] of evidence
ACE inhibitors[3,4]	Medium	Avoid excessive potassium intake	Pharmacodynamic interaction	Risk of hyperkalaemic adverse effects	3/D
Acitretin[5]	Unknown	With a fatty meal	Absorption favoured by bile secretion	Possible increase in drug effect	1++/B
Alendronic acid[6]	High	Without food or milk	Chelation	High risk of treatment failure	2++/B
Albendazole[7,8]	High	With a fatty meal	Increased solubility with fat intake	Only relevant for treatment of systemic infections	2++/B
Ampicillin[9-13]	Medium	Without food	Acid lability	Risk of treatment failure when given in low dosage	1++/A
Atovaquone[14-17]	Medium	With a fatty meal	Increased solubility with fat intake	Increased likelihood of achieving target concentrations against PCP infection	1++/A
Azithromycin capsules[18]	High	Without food	Acid lability	Risk of treatment failure	1++/A
Captopril[19-22]	Low	None	Decreased absorption	No changes in humoral or haemodynamic effects	1+/B
Carbamazepine tablets[23]	Medium	With a consistent relationship to meals	Absorption favoured by bile secretion	To avoid fluctuations in drug effect	2++/C
Cefuroxime axetil[24-28]	Low	With a meal	Dependent on gastric acid for solubility	Treatment failure unlikely	2+/C
Cephalexin[29]	Low	Without milk/formula	Acid lability	Only relevant in young children. No change in antibacterial activity	2+/B
Ciprofloxacin[30]	High	Without milk	Chelation	Risk of treatment failure	1++/A
Clodronic acid[31]	High	Without food or milk	Chelation	High risk of treatment failure	1++/A
Clofazimine[32]	Unknown	With food	Unknown	Therapeutic drug levels may be reached sooner	1++/B
Didanosine[33-35]	High	Without food	Acid lability/chelation	Risk of treatment failure in adults only	1++/A
Digoxin[36,37]	High	With a consistent dietary fibre intake	Binding to fibre	Change in dietary fibre intake may require dosage adjustment	1++/A
Doxycycline[38]	Low	Without milk	Chelation	Treatment failure unlikely	2++/B
Erythromycin stearate[39-45]	Medium	Without food	Acid lability	Little risk of treatment failure	2++/B
Erythromycin enteric coated[41,43,45-48]	High	Without food	Acid lability	Risk of treatment failure	2++/B
Erythromycin ethylsuccinate[29,49]	Low	With food	Unknown	Only relevant in young children. No change in antibacterial activity	2++/B
Etidronic acid[50,51]	High	Without food or milk	Chelation	High risk of treatment failure	2++/B
Furosemide[52-55]	Low	Without food	Reduced intestinal absorption	Possible reduction in diuretic response	1++/A
Ganciclovir[56,57]	Unknown	With food	Unknown	Possible increase in drug effect	2++/B
Griseofulvin[58-62]	High	With a fatty meal	Absorption favoured by bile secretion	Taking with food is required to avoid treatment failure, particularly in children	2++/B
Halofantrine[63]	High	Without food	Absorption favoured by bile secretion	Taking with food may result in severe toxicity	1++/B
Hydralazine[64-69]	Medium	With a consistent relationship to meals	Unknown	To avoid fluctuations in bioavailability and drug effect	1++/A

Continued next page

Table I. Contd

Drug or class	Clinical relevance	Dietary recommendation	Proposed mechanism of interaction	Consequences and qualifications of interaction	Level[a]/grade[b] of evidence
Indinavir[70]	High	Without food	Food may cause precipitation	High risk of treatment failure	1++/B
Isoniazid[71-75]	Medium	Without food	Acid lability	Risk of treatment failure	1++/A
Isotretinoin[76]	High	With a consistent relationship to meals	Increased solubility with fat intake	To avoid fluctuations in drug effect	1++/A
Itraconazole capsules[77-81]	High	With a meal	Dependent on gastric acid for solubility	Improved clinical response	1++/A
Itraconazole solution[82,83]	High	Without food	Food increases first-pass metabolism	Advantageous in anorexic patients	1++/A
Levodopa[84-88]	Medium	Without food	Competition with food components	Risk of insufficient drug response	2++/B
Lovastatin[89,90]	High	With a (low-fibre) meal	Increased solubility with fat intake	Increased drug effect. A high-fibre diet may result in treatment failure	2++/C
MAO inhibitors[91,92]	High	With a tyramine-restricted diet	Blocked deamination of dietary pressor amines	Risk of hypertensive crisis	3/D
Mefloquine[93]	Medium	With food	Increased solubility with fat intake	Mainly relevant when used for prophylaxis	1++/B
Melphalan[94,95]	High	Without food	Competition with dietary amino acids	Risk of treatment failure	2+/C
Methotrexate[96-98]	Medium	Without food	Unknown	Risk of treatment failure in children only	1++/A
Mercaptopurine[99-101]	High	Without food	Food causes oxidation into inactive metabolites	Risk of treatment failure	2++/B
Misoprostol[102,103]	Low	With food	Food reduces absorption rate	Reduced risk of systemic adverse effects	2+/B
Nifedipine capsules/ tablets[104-107]	Medium	With food	Food reduces absorption rate	Reduced risk of adverse effects	1++/A
Nifedipine sustained release[108-110]	Medium	With a consistent relationship to meals	Absorption favoured by bile secretion	Taking with food increases hypotensive effect	2++/C
Norfloxacin[111,112]	High	Without milk	Chelation	Risk of treatment failure	2++/B
Ondansetron[113]	Low	With food	Unknown	None	1++/A
Penicillamine[114-116]	High	Without food or milk	Chelation	High risk of treatment failure	1++/B
Phenoxymethyl-penicillin[29,37,117-119]	Low	Without food	Acid lability	Treatment failure unlikely	2++/B
Perindopril[120]	High	Without food	Food inhibits conversion into active metabolite	Significant decrease in ACE inhibition	1++/B
Phenytoin[121-124]	High	Without enteral feeds	Chelation/binding to protein components	High risk of treatment failure	2++/B
Pravastatin[125]	Low	None	Food increases conversion into inactive metabolite	No changes in lipid-lowering capacity	1++/A
Quinidine sulfate[126]	Medium	With food	Food reduces absorption rate	Reduced risk of adverse effects	1++/A
Rifampicin[75,127-132]	Low	Without food	Food increases first-pass metabolism	Treatment failure unlikely	1++/B
Saquinavir[133,134]	High	With a meal	Food increases dissolution	High risk of treatment failure	2++/C
Spironolactone[135,136]	High	Avoid excessive potassium intake	Pharmacodynamic interaction	Risk of hyperkalaemic adverse effects	3/D

Table I continued

There are only a few examples of pharmacodynamic interactions in which food or food derivatives affect the drug action at a receptor level.[155]

1.1 Characteristics of the Drug

Physical and chemical characteristics of a drug are important factors in its potential for interactions with food. Different drugs within the same drug group or different formulations of identical drugs can have different chemical characteristics and thereby completely different food-drug interactions. However, it is generally not possible to exactly predict food-drug interactions only from knowledge of the physicochemical properties of the drug, and interaction studies of drug pharmacokinetics and effects with or without concomitant food intake are required.[156]

1.2 Characteristics of the Meal

The development of food-drug interactions may depend on the size and the composition of a meal as well as the exact timing of drug intake in relation to a meal.[155] For example, the bioavailability of lipophilic drugs is often increased by a high fat content, either because of increased drug solubility (e.g. albendazole and isotretinoin) or stimulation of bile secretion (e.g. griseofulvin and halofantrine). Alternatively, a high fibre content may reduce the bioavailability of certain drugs (e.g. digoxin and lovastatin) because of binding to the fibre. However, these conditions are often poorly examined, and many different definitions of fasting are used. Unless stated otherwise, the term fasting in this review means no food intake for at least 1 hour before and at least 2 hours after drug intake.

1.3 Pharmacokinetic Effect Parameters

The bioavailability and the effect of most drugs are correlated, making changes in bioavailability an important effect parameter of food-drug interactions. Bioavailability is dependent on absorption and first-pass metabolism. The most important pharmacokinetic food-drug interactions are caused by changes in the absorption of a drug because of

Tacrine[137]	Unknown	With a meal	Food decreases first-pass metabolism	Likely improvement in therapeutic efficacy	1++/B
Tacrolimus[138]	High	With a consistent relationship to meals	Increased solubility with fat intake	To avoid fluctuations in drug effect	1++/B
Tetracycline[139-142]	High	Without food or milk	Chelation	High risk of treatment failure	2++/B
Theophylline ultraslow release[143-145]	Medium	Without food	Dose-dumping	Risk of toxicity. Only applies to older preparations (see section 11.1)	1++/A
Troglitazone[146]	Unknown	With a meal	Absorption favoured by bile secretion	Likely improvement in therapeutic efficacy	1+/B
Warfarin[147-150]	Medium	Avoid excessive intake of vitamin K	Direct antagonism by vitamin K-content in food	Only relevant with a continuous daily ingestion of vitamin K-rich food	1+/B
Zalcitabine[151]	Unknown	Without food	Food reduces absorption	Treatment failure unlikely	1++/A
Ziprasidone[152,153]	Unknown	None	Increased solubility with fat intake	Undetermined	1++/B
Zuclopenthixol[154]	Low	None	Food reduces first-pass metabolism	None	1++/B

a Evidence level: level 1 includes evidence from randomised controlled trials; level 2 includes evidence from other controlled studies; level 3 includes case reports and case series. ++ and + apply, respectively, to a very high and a high quality rating of the studies.

b Evidence grade: grade A is directly based on level 1 evidence; grade B is directly based on level 2 evidence or extrapolated from level 1 evidence; grade C is extrapolated from level 2 evidence; grade D is based on level 3 evidence.

MAO = monoamine oxidase; **PCP** = *Pneumocystis carinii* pneumonia; **SIGN** = Scottish Intercollegiate Guidelines Network.

chemical reactions between the drug and the food (e.g. chelation) or to the physiological response to food intake (changes in gastric acidity, bile secretion or gastrointestinal motility).

Food-drug interactions that only affect the rate of drug absorption are common but rarely of clinical importance. However, with some drugs a rapid absorption resulting in high peak drug concentrations may be undesirable because of the development of concentration-dependent adverse effects (e.g. misoprostol and nifedipine capsules). With some other drugs (including many antibacterials), the drug effect depends on the time for which drug concentrations exceed a certain threshold concentration, which for antibacterials is termed the minimum inhibitory concentration (MIC). If absorption of such a drug is sustained as well as decreased, the duration of therapeutic drug concentrations (and thereby the drug effect) may be unchanged (e.g. phenoxymethylpenicillin [penicillin V]).

Interactions affecting metabolism, distribution or elimination are not very common, apart from interactions with grapefruit juice. Grapefruit juice contains potent inhibitors of the cytochrome P450 (CYP) 3A4 system and may markedly increase the bioavailability of drugs that undergo significant presystemic metabolism by CYP3A4.[157]

1.4 Clinical Effect Parameters

The relationship between pharmacokinetic parameters and pharmacological effects is not always simple, and generally food-induced changes in bioavailability of a drug may only be taken as an indication of a food-drug interaction. The clinical relevance of a given food-drug interaction can only be evaluated if the impact of food intake on the pharmacological effect of the drug is quantified. The relevant effect parameters will depend on the type of drug (e.g. antibacterial, antihypertensive, lipid-lowering or anticoagulant) and, for many drugs, the pharmacological effect is not directly quantifiable. In this review we have tried to provide both a relevant pharmacokinetic effect parameter (usually bioavailability) and an evaluation of the clinical significance of the given food-drug interaction.

2. Agents Affecting the Alimentary Tract and Metabolism

Administration of the synthetic prostaglandin analogue misoprostol with food reduces its rate of absorption and consequently the height of its initial peak plasma concentration by 63% without affecting its bioavailability.[102] Because the systemic adverse effects associated with misoprostol are related to high peak drug concentrations, taking the drug with food decreases the incidence of adverse effects, while maintaining the desired drug effect.[103]

The bioavailability of the antiemetic ondansetron is increased by 14% when administered after a meal, which is probably not clinically significant.[113]

Taking the oral antidiabetic agent troglitazone with or shortly after a meal increases its bioavailability by 59%, which may be reflected in an improved insulin action-enhancing effect.[146]

3. Agents Affecting the Blood and Blood Forming Organs

Intake of a regular meal does not affect the bioavailability of warfarin.[158] However, the pharmacodynamic effect of warfarin may be directly antagonised by the ingestion of foodstuffs rich in vitamin K such as cabbage, broccoli, liver and certain dietary supplements.[147-150] A single excessive intake of vitamin K-rich food has no clinically significant impact on the anticoagulant effect of warfarin; however, a continuous daily ingestion of high amounts of vitamin K-rich food for one week may lead to warfarin resistance requiring dosage adjustments.[147,150] Despite being low in vitamin K, avocado intake has been reported to cause warfarin antagonism, although the exact mechanism is obscure.[159] Since phenprocoumon is pharmacodynamically similar to warfarin, it is assumed to have similar interactions with vitamin K-rich food.

4. Agents Affecting the Cardiovascular System

4.1 Cardiac Glycosides and Antiarrhythmics

Ingestion of a regular meal does not affect the bioavailability of digoxin[36,160-162] but ingestion of a high amount of dietary fibre as found in fibre preparations reduces the bioavailability of digoxin by 16 to 32%.[36,163] Due to the narrow therapeutic index of digoxin, a high-fibre diet (such as that used as an intervention for patients with hypercholesterolaemia) may result in treatment failure requiring dosage adjustment.

The bioavailability of the sustained release formulation of quinidine gluconate has been shown to be unaffected[164] or marginally increased (by 10 to 12%) when taken with food; however, there is considerable interindividual variability.[165] Food intake does not affect the bioavailability of quinidine sulfate, but it slows the absorption rate.[126,166] The adverse effects of quinidine have been related to high initial peak drug concentrations, and postprandial administration of quinidine sulfate is associated with a reduction in adverse effects.[126]

4.2 Antihypertensives

Findings on the effect of food on the bioavailability of hydralazine are conflicting. One study showed a 104 to 145% increase in bioavailability when hydralazine was taken with a meal (reduced first-pass metabolism).[167] In two subsequent studies, hydralazine bioavailability was either unaffected[65] or only marginally increased by food.[66] In contrast, the three most recent studies all showed that food intake reduces the bioavailability of hydralazine by 46 to 55%;[67-69] in one study this was associated with a significant reduction in vasodepressor effect.[68] Coadministration of a bolus of an enteral nutrient reduces the bioavailability of hydrazine by 62%, whereas no interaction is seen with a slow infusion of an enteral nutrient.[69] Overall, adverse fluctuations in the effect of hydralazine may best be prevented by taking the drug with a consistent relation to meals.

4.3 Diuretics

The bioavailability of furosemide (frusemide) is reduced by 16 to 45% when taken with food.[52-55] In one study, this was associated with a reduction in diuretic response,[54] whereas diuresis in another study was almost unaffected.[53] Overall, the food-drug interaction with furosemide is not considered to be of major clinical importance, but it may explain why some individuals with apparent furosemide resistance may respond to bumetanide. No food-drug interaction has been demonstrated with bumetanide.[52]

When potassium-sparing diuretics are used, a high intake of potassium-rich foodstuffs such as bananas and spinach may result in hyperkalaemia.[135] In particular, severe hyperkalaemia with serious cardiac arrhythmia has developed after excessive use of potassium-containing salt substitutes in patients treated with spironolactone.[136]

4.4 Calcium Channel Antagonists

The effect of food on the absorption of nifedipine depends on the formulation. Since the haemodynamic response to nifedipine significantly correlates with its plasma concentration, larger fluctuations in concentration are undesirable, and adverse effects such as hypotension, flushing and headache are seen with high peak drug concentrations.[105] Administration of nifedipine capsules or tablets with a meal reduces the height of the initial peak plasma concentration and thereby the risk of developing adverse effects, while the bioavailability and desired clinical effect are maintained.[104-107] Food increases the bioavailability of nifedipine sustained release preparations by 28 to 31%[108-110] which is reflected in a significantly increased hypotensive effect.[108] Food does not significantly affect the bioavailability of nifedipine from modified release (e.g. Adalat Retard®[1]) or controlled release (e.g. Adalat® Oros) formulations.[168,169]

Felodipine provides the original example of an interaction between grapefruit juice and a drug.

1 Use of tradenames is for product identification purposes only and does not imply endorsement.

Grapefruit juice increases the bioavailability of felodipine by 284% by inhibiting its first-pass metabolism, and the clinical effect on blood pressure and heart rate is doubled.[170] A similar effect of grapefruit juice is seen with other dihydropyridine calcium channel antagonists, but not with diltiazem or verapamil, even though these are also substrates for CYP3A4.[157,170-172]

4.5 ACE Inhibitors

Food intake decreases the bioavailability of captopril by 42 to 56%.[19,20] This interaction has limited clinical relevance though because the haemodynamic and humoral effects of captopril are not significantly affected by food.[20-22] Food intake also decreases the bioavailability of perindopril by 35% which is associated with a clinically significant decrease in ACE inhibition.[120] The bioavailability of cilazapril,[173] enalapril[174] and lisinopril[175] is unaffected by food intake.

Hyperkalaemia is a frequent complication of therapy with all ACE inhibitors and may be aggravated by intake of potassium-rich foodstuffs or salt substitutions.[3,4]

4.6 Serum Lipid-Lowering Agents

The various hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitors have very different chemical and pharmacokinetic properties. The bioavailability of lovastatin increases by 50% when taken with a regular meal; this is reflected in an increased drug effect.[90] In contrast, the ingestion of fibres or fruit as part of a lipid-lowering diet may strikingly reduce the absorption of lovastatin and increase the risk of treatment failure.[89]

The bioavailability of pravastatin is reduced by 31% when taken with food; however, since its lipid-lowering efficacy is unchanged the interaction is not clinically important.[125] For atorvastatin[176,177] and fluvastatin,[178] bioavailability and lipid-lowering efficacy are unaffected by food intake.

Excessive ingestion of grapefruit juice increases the bioavailability of lovastatin, atorvastatin and simvastatin by 1400, 200 and 1500%, respectively, by inhibiting their first-pass metabolism. This may lead to drug accumulation and the possible development of adverse effects.[179-181] Pravastatin and fluvastatin are not exclusively metabolised by CYP3A4 and are consequently not subject to drug–grapefruit juice interactions.[157,180]

5. Dermatological Agents

The bioavailability of the anti-acne agent isotretinoin is increased by 72 to 86% when administered with or shortly after a meal.[76] Because isotretinoin dosage is titrated according to drug effect and the appearance of adverse effects, the drug should be taken with a consistent relationship to meals.

Food intake increases the bioavailability of the antipsoriatic agent acitretin by 91% and reduces the interpatient variability in bioavailability.[5] Accordingly, coadministration of acitretin with food may be preferred.

6. Anti-infectives for Systemic Use

6.1 Tetracyclines

The bioavailability of tetracycline is reduced by 46 to 57% when taken with food, by 50 to 65% when taken with dairy products and by up to 81% when taken with iron supplements because of chelation.[140-142] This interaction may result in treatment failure in cases involving pathogens with a moderate resistance to tetracycline.[142] Even the use of a small volume of milk in tea or coffee is sufficient to cause a 49% reduction in tetracycline bioavailability.[139]

The bioavailability of doxycycline is, at most, marginally affected by regular food intake, but is reduced by 30% when taken with dairy products.[38,141,142] In spite of milk intake, doxycycline concentrations are usually well above the MIC for most pathogens, and the interaction is of minor clinical consequence. With all tetracyclines there is a high likelihood of the formation of chelates with polyvalent cations (e.g. iron, calcium, magnesium and aluminium) that may also be contained in certain dietary supplements.[141]

6.2 Penicillins

Ingestion of food,[117-119] dietary fibre[37] or milk/formula[29,118] reduces the bioavailability of phenoxymethylpenicillin by 25 to 37%, but also causes a more sustained rate of absorption. Since phenoxymethylpenicillin is typically substantially overdosed, the duration of bactericidic drug concentrations in blood and saliva is unchanged by food, and the interaction is of minor clinical significance.[29,119]

Food intake reduces the bioavailability of ampicillin by 22 to 50%.[9,11-13] Since the rate of absorption is unchanged by food, the duration of bactericidic ampicillin concentrations is considerably reduced and treatment failure may occur.[10,12] However, the absorption of ampicillin suspension is unaffected by milk/formula.[29]

The bioavailability of amoxicillin is unaffected by ingestion of regular food[9,10,12] or milk/formula,[182] but is reduced by 21% by a high-fibre diet, which is probably not clinically significant.[183]

No food-drug interaction has been demonstrated with pivampicillin.[11,184]

6.3 Cephalosporins

The bioavailability of cefuroxime axetil is increased by 28 to 70% when taken with food[24,26-28] and by 25 to 97% when taken with milk.[25] In the recommended dosages, this interaction is of minor clinical significance since sufficient antibacterial concentrations of cefuroxime are usually reached independently of feeding status.[25,26] In older children and adults, the bioavailability of cephalexin is unaffected by food intake.[185,186] In young children, the bioavailability of cephalexin is reduced by 40% when taken with milk.[29] The clinical relevance of this interaction is limited because antibacterial drug concentrations of cephalexin are not reached in the majority of young children, irrespective of feeding status.[29]

6.4 Macrolides

Because erythromycin base is acid labile, various formulations of erythromycin as salts or esters or as different types of coated tablets have been proposed to enhance the oral bioavailability of erythromycin by improving its acid stability. The effect of food on the pharmacokinetics of erythromycin depends on the formulation and is very complex. The majority of studies have shown that the bioavailability of erythromycin stearate is reduced by 18 to 79% when taken with or shortly after a meal.[39-45] In contrast, one study showed no significant effect of food intake,[187] whereas another study found that the bioavailability of erythromycin stearate increased by 28% when taken shortly before a meal.[47] In adults, the bioavailability of erythromycin ethylsuccinate is reduced by 35% when taken with food; however, erythromycin concentrations well above MIC for most pathogens are achieved irrespective of feeding status.[188] In children, food increases the bioavailability of erythromycin ethylsuccinate by 100 to 185%,[29,49] but clinical response[49] and saliva erythromycin concentrations are unchanged.[29] The bioavailability of erythromycin acistrate is unaffected by food intake.[46,189]

The bioavailability of erythromycin from enteric coated tablets was not significantly affected by food intake in two studies,[47,190] whereas two other studies found marked reductions in erythromycin bioavailability (concentrations were undetectable in eight out of ten participants).[45,46] Similarly, the bioavailability of erythromycin from enteric coated pellets was unaffected by food intake in one study,[41] but was reduced by 25 to 83% in three other studies (subtherapeutic concentrations were measured in nine out of 14 individuals).[41,43,47] Finally, the bioavailability of erythromycin from a film-coated particle-in-tablet formulation was reduced by 72% in one study when taken with food (concentrations were undetectable in 7 out of 27 individuals).[48]

Giving a general recommendation for erythromycin is difficult. With standard dosages of the drug the risk of treatment failure is limited, and in

most cases taking erythromycin with meals is preferred by the patient because it alleviates adverse gastrointestinal effects. However, enteric coated erythromycin formulations are probably best taken without food in order to minimise the gastric residence time.

The bioavailability of azithromycin capsules is reduced by 50% when taken with food.[18] In contrast, the bioavailability of azithromycin tablets[191,192] or suspension[192] is unaffected by food intake. Thus, any food-drug interaction of azithromycin is restricted to the capsule formulation. No food-drug interaction has been demonstrated with clarithromycin or roxithromycin.[187,193,194]

Ingestion of grapefruit juice increases the bioavailability of erythromycin[195] by 49% (inhibition of first-pass metabolism) but does not affect clarithromycin.[196]

6.5 Quinolones

The bioavailability of ciprofloxacin is unchanged when taken with food, but reduced by 30 to 36% when taken with dairy products because of chelation.[30,197-199] Since ciprofloxacin concentrations resulting from standard dosages of ciprofloxacin often only marginally exceed the MIC for modestly susceptible pathogens, this interaction may result in treatment failure.[30] Likewise, the bioavailability of norfloxacin is reduced by 38 to 52% when taken with dairy products.[111,112] The bioavailability of ofloxacin is unaffected by concomitant ingestion of food or dairy products.[199-203] The cation content (e.g. iron, magnesium and zinc) of certain enteral feeds may also cause chelation with quinolones.[204]

6.6 Antimycotics

The bioavailability of itraconazole capsules is increased by 31 to 163%[77,78,80,81] when taken with a meal (this increase is associated with an improved clinical response).[79] The interaction is ascribed to the effect of gastric acid secretion because itraconazole, a weak base, is only soluble at acidic pH. In contrast, the bioavailability of itraconazole solution (hydroxypropyl-β-cyclodextrin) is enhanced in the fasting state and reduced by 28 to 30% when taken with food.[82,83] Consequently, this formulation may be advantageous in seriously ill anorexic patients who are not able to ingest adequate quantities of food.

The effect of food intake on ketoconazole is rather obscure, since one study showed a tendency towards an increase in bioavailability, but another showed a tendency towards a decrease in bioavailability.[205,206] In a third study, the bioavailability of ketoconazole decreased by 40% when taken with food.[207] Finally, a fourth study found that the bioavailability of ketoconazole tended to be increased by intake of a high-fat meal, but to be reduced by intake of a high-carbohydrate meal.[208] Overall, the evidence does not support that concomitant food intake may lead to ketoconazole treatment failure.[205]

The absorption of itraconazole and ketoconazole is severely impaired in patients with achlorhydria[208] (commonly seen in AIDS gastropathy). This may be counteracted by the coadministration of an acidic beverage such as cola which increases the bioavailability of these drugs by 38 to 220% in these patients, making their oral treatment possible.[209-211] However, grapefruit juice cannot be used for this purpose since the bioavailability of itraconazole is either unaffected or even paradoxically reduced by 43% when taken with grapefruit juice.[212,213]

The bioavailability of griseofulvin is increased by 37 to 120%[58,61,62] when taken with a fat-containing meal, but not when taken with carbohydrates or protein.[59] In one study, a low-fat and a high-fat meal increased griseofulvin bioavailability by 70 and 120%, respectively, reflecting a direct dependence on fat content.[62] In children, concomitant ingestion of milk increases the bioavailability of griseofulvin by up to 900%, and there is risk of griseofulvin treatment failure when taken in the fasted state.[60]

6.7 Antimycobacterials

Food intake decreases the bioavailability of isoniazid by 12 to 43% which may lead to treatment

failure.[71-75] Because isoniazid is also a monoamine oxidase inhibitor (MAOI; see section 9.3), caution should be taken with tyramine-rich foodstuffs.[214,215]

The bioavailability of rifampicin is reduced by up to 26% when taken with food, but since the duration of bactericidic drug concentrations is unchanged, the risk of treatment failure is limited.[75,127-131] However, eight cases have been reported in which rifampicin treatment failure was suspected because of coadministration with a meal, yet measurements of drug concentration to substantiate these observations were not performed.[132] Ethambutol may be taken without regard to meals.[216,217]

Food intake increases the bioavailability of the anti-leprosy agent clofazimine by 62% which may reduce the treatment time needed to achieve therapeutic drug concentrations.[32]

6.8 Antivirals

The bioavailability of ganciclovir is increased by 20 to 22% when taken with food which, due to the low oral bioavailability of the drug, may be clinically important.[56,57]

In adults, the bioavailability of the reverse transcriptase inhibitor didanosine is reduced by 41 to 55% when taken with food and this is associated with a high risk of treatment failure.[33-35] However in HIV-infected children, the bioavailability of didanosine is unaffected by food intake.[218] Food intake causes a 14% reduction in zalcitabine bioavailability which is not expected to be of clinical importance.[151] The absorption of zidovudine, lamivudine and abacavir is delayed and prolonged, but otherwise unaffected by food intake; this is of no clinical significance.[219-223]

Coadministration of the protease inhibitor saquinavir with a meal dramatically increases its bioavailability by 600 to 1800%,[133,134] whereas administration in the fasted state resulted in unmeasurable drug concentrations in four out of eight patients with an associated high risk of treatment failure.[133] When a high dose (600mg) of saquinavir is administered, a heavy meal causes twice the increase in bioavailability as a light meal.[134] Also, grapefruit juice may increase the bioavailability of saquinavir by 53% by inhibiting its first-pass metabolism by CYP3A4.[157] In contrast, the bioavailability of indinavir is reduced by 78% when taken with food and this is reflected by a high risk of treatment failure.[70]

7. Antineoplastic and Immunomodulating Agents

7.1 Antineoplastic Agents

Food intake decreases the bioavailability of the alkylating agent melphalan by 43 to 55%[94,95] which in one study resulted in a patient with undetectable drug concentrations and treatment failure.[95] The bioavailability of chlorambucil was reduced by 34% when taken with food in one study[224] but was unaffected by food in another study.[225]

In adults, the bioavailability of the antimetabolite mercatopurine is reduced by 65% when it is administered with food (undetectable drug concentrations were reported in two out of seven patients in one study) with subsequent risk of treatment failure.[99] In children, food intake reduced the bioavailability of mercaptopurine by 27% in one study [101] but in another study it was unaffected (although considerable interindividual variability was reported).[100]

In children, the bioavailability of methotrexate is reduced by 19 to 28% when taken with food which may be clinically significant.[96-98] In contrast, methotrexate bioavailability in adults is unaffected by food.[226-228]

7.2 Immunosuppressive Agents

The bioavailability of the microemulsion formulation of cyclosporin (Sandimmune Neoral®) is unaffected[229,230] or marginally reduced[231] by food intake. The effect of food intake on the conventional cyclosporin formulation (Sandimmune®) exhibits considerable inter- and intrapatient variability. In two studies, the bioavailability of conventional cyclosporin increased by 37 to 267%

when taken with food,[232,233] whereas it was unchanged in two other studies.[229,230]

The bioavailability of tacrolimus is reduced by 33% when taken with food, hence the drug should be taken with a consistent relationship to meals in order to avoid adverse fluctuations in its concentrations.[138]

Ingestion of grapefruit juice may increase the bioavailability of cyclosporin by 47 to 60% and presumably that of tacrolimus as well, since both are CYP3A4 substrates.[157,234,235] Consequently, ingestion of grapefruit juice may lead to the development of toxic adverse effects. The effect is highly variable and unpredictable, so coadministration of grapefruit juice for the purpose of achieving cyclosporin dosage reduction is not recommended.

8. Agents Affecting the Musculo-Skeletal System

8.1 Anti-inflammatory and Antirheumatic Agents

Concomitant food intake will delay but not significantly reduce the absorption or the effect of most nonsteroidal anti-inflammatory drugs (NSAIDs).[236] Unless a rapid drug action is required, ingestion of NSAIDs with food is often preferred because it reduces local gastrointestinal adverse effects.

Penicillamine is a strong chelating agent. Consequently, the bioavailability of penicillamine is decreased by 51 to 59% when taken with food and by 82% when taken with iron supplements. This is associated with a reduced clinical effect including reduced copper excretion, which is relevant to its use in Wilson's disease.[114-116]

8.2 Agents Affecting Mineralisation

The effect of food intake on bisphosphonates is very pronounced because these agents have an exceptionally high affinity for chelation with dietary divalent cations. The bioavailability of clodronic acid is reduced by 31% when taken half an hour before a meal, by 90% when taken with a meal, and by 66% when taken even 2 hours after a meal.[31] Similarly, the bioavailability of alendronic acid is reduced by 85 to 90% when taken with a meal or within at least 2 hours of a meal; this is reflected in a high risk of treatment failure.[6] Even the concomitant ingestion of coffee or orange juice causes a 60% decrease in alendronic acid bioavailability.[6] Consequently, clodronic acid and alendronic acid should be taken with plain water on an empty stomach at least 30 minutes to 1 hour before a meal, preferably breakfast. Food intake causes 100% malabsorption of etidronic acid, whereas the clinical effect is maintained when etidronic acid is taken midway through a 4-hour fast.[50,51]

9. Agents Affecting the Nervous System

9.1 Antiepileptic Drugs

One study showed a 16% decrease in phenytoin bioavailability when taken with food, whereas another showed a 27% increase.[237,238] A marked interindividual variation was observed, in that the increase found in the second study entirely attributable to two out of eight individuals (65 and 109% increase, respectively).[238] The bioavailability of phenytoin is unaffected by ingestion of milk.[239] In contrast, coadministration with enteral feeds causes a 72% reduction in the serum-concentration of phenytoin, probably because of chelation with divalent cations and binding to protein components in the enteral formulas.[121,122,124] Consequently, there is a high risk of treatment failure when enteral feeding is instituted in patients receiving phenytoin, but also of sudden toxicity when the enteral feeding is discontinued without phenytoin dosage reduction.[121] Coadministration of phenytoin and a jejunostomy feed via a jejunostomy tube has resulted in nearly 100% malabsorption of phenytoin.[123]

The bioavailability of carbamazepine tablets increases by 22% when taken with food and, because there is pronounced interindividual variation in this interaction, taking carbamazepine without a consistent relationship to meals may result in adverse fluctuations in the drug concentration.[23] In contrast, the bioavailability of carbamazepine from

the newer slow release[240] and controlled release[241] formulations is unaffected by food intake. Grapefruit juice increases the bioavailability of carbamazepine by 41% by inhibiting first-pass metabolism by CYP3A4; this may lead to the development of adverse effects.[242]

No clinically significant food-drug interaction with oxcarbazepine has been demonstrated.[243]

9.2 Anti-Parkinsonian Agents

The bioavailability of levodopa is unaffected or marginally decreased (by up to 27%) when taken with a meal; this may be associated with a delayed, curtailed or insufficient drug response.[85-88,244] The protein content of the meal does not appear to influence the bioavailability.[244] Traditionally, levodopa has been given with meals to limit adverse gastrointestinal effects and to achieve more sustained plasma concentrations; however, with the introduction of drug combinations with decarboxylase inhibitors, this recommendation has become less relevant.[85] In patients with Parkinson's disease who also have severe constipation, a high-fibre diet caused a 71% increase in levodopa bioavailability via an increase in gastrointestinal motility.[84]

In order to reach the dopamine receptors in the brain, levodopa has to penetrate the blood-brain barrier mediated by a selective carrier for all large neutral amino acids (LNAA). In patients with sudden oscillations in their clinical response to levodopa (the 'on-off' phenomenon), ingestion of protein with a high LNAA content may reverse the clinical effect of levodopa by competitive inhibition of the LNAA carrier.[87,245,246] Consequently, an alteration in drug distribution rather than absorption is the most likely cause of any food-induced alterations in the clinical response to levodopa. However, a high protein consumption (2g per kg of bodyweight) is required for this interaction to be clinically relevant so diets within the recommended daily allowance of protein (0.8g per kg of bodyweight) have no major effect.[247,248]

9.3 Antipsychotics and Antidepressants

Taking zuclopenthixol with a meal increases its bioavailability by 26%. However, this is of doubtful clinical significance because the oral bioavailability of zuclopenthixol is usually sufficiently high irrespective of feeding status.[154]

The bioavailability of ziprasidone is increased by 43 to 97% when taken with food.[152,153] The clinical significance of this interaction has not been determined.

MAOIs are well known to be associated with a risk of hypertensive crisis after the ingestion of tyramine-containing foodstuffs.[91] Almost 80% of all reported cases can be attributed to cheese ('cheese reaction').[91] The incidence of the reaction is approximately 4% in patients treated with MAOI, but it is probably even lower with appropriate dietary restrictions.[92,249] In a series of 25 patients with MAOI-related hypertensive crisis, four cases were complicated by intracranial haemorrhage (resulting in one fatality).[92]

9.4 Antidementia Agents

The bioavailability of tacrine is reduced by 26% when taken with a meal and by 21% when taken even 2 hours after a meal which is likely to reduce the therapeutic efficacy.[137] However, taking tacrine in the fasted state is frequently not tolerated by patients because of adverse gastrointestinal effects.[137]

10. Antiparasitic Agents

10.1 Antiprotozoal Agents

The bioavailability of the antimalarial agent mefloquine is increased by 33 to 40% when taken with food.[93] Because its oral bioavailability is high overall, this interaction is of limited consequence in the treatment of malaria, but it may be of significance when using mefloquine for once-weekly chemoprophylaxis.[93]

Food intake very significantly increases the bioavailability of halofantrine by 190% and its peak concentration by over 500%.[63] This may lead to

toxic halofantrine concentrations with a high risk of cardiotoxicity (e.g. arrhythmias and even cardiac arrest). Consequently, halofantrine should be used cautiously and never be taken with food.

Food intake increases the bioavailability of atovaquone from tablets by 200 to 290%[17] and from various suspensions by 26 to 174%,[14-17] which is mainly attributable to the fat content of the meal.[17] In patients with HIV, target concentrations for the treatment of *Pneumocystis carinii* pneumonia (PCP) are more consistently achieved when atovaquone is administered with food or a nutrition supplement with a moderate fat content.[14,16]

10.2 Anthelmintics

The bioavailability of albendazole is increased by 295 to 299% when taken with food which enhances its chemosterilant properties against systemic parasitic infections.[7,8] However, administration of albendazole in the fasted state may be appropriate and even preferable for the treatment of intraluminal intestinal parasites where a systemic effect is not required.[8]

The bioavailability of mebendazole is not significantly affected by food intake.[250]

11. Agents for the Respiratory System

11.1 Anti-Asthmatics

The bioavailability of non-retarded and sustained release formulations of theophylline are largely unaffected by concomitant food intake.[251-258] However, a high-protein/low-carbohydrate diet may cause an increase in the hepatic clearance of theophylline.[259]

The so-called ultraslow releasing formulations of theophylline are designed to be given once daily and should ideally release the drug dose at a constant rate over 24 hours.[260] For first generation drugs of this type (e.g. Theo-24® and Uniphyl®), food intake increases the bioavailability of theophylline by 43 to 81% and may cause 'dose-dumping' defined by a sudden delivery of a substantial part of the dose.[143-145] In a study of the original once daily theophylline preparation (Theo-24®), concomitant food intake caused 'dose-dumping' in six of eight participants, four of whom showed theophylline toxicity.[143] The newer once daily theophylline preparations[261,262] (e.g. Dilatrane® and Uni-Dur®) and especially the dissolution rate-limited oral extended release formulation[263] (e.g. Monospan®) may be taken without regard to food.

11.2 Antihistamines

Terfenadine undergoes almost complete presystemic metabolism by CYP3A4. Inhibition of CYP3A4 by ingestion of grapefruit juice leads to detectable systemic concentrations of the parent compound terfenadine which has arrhythmogenic properties (it causes prolongation of the QTc interval that may develop into ventricular arrhythmias).[264-266] When the sudden unexpected death of a 29-year old healthy man was ascribed to a drug-grapefruit juice interaction with terfenadine, the drug was voluntarily removed from the US market, albeit with a different motivation.[267] However, terfenadine remains available in several other countries. Similar interactions may be seen with the potentially cardiotoxic antihistamine, astemizole, that was voluntarily removed and subsequently withdrawn from the market, partly because of reports of serious cardiovascular toxicity.[268]

12. Conclusions

There is considerable variation in the extent and clinical relevance of food-drug interactions. The most important interactions are those associated with a high risk of treatment failure arising from a significantly reduced bioavailability in the fed state (e.g. tetracycline, indinavir and bisphosphonates). For several drugs, the pharmacokinetic evidence of a food-drug interaction is not accompanied by any major changes in clinical effect (e.g. pravastatin, phenoxymethylpenicillin and furosemide). For other drugs, food-drug interactions may increase drug bioavailability and thereby drug effect (e.g. albendazole, griseofulvin and saquinavir).

Such an increase is usually desirable, but may also lead to serious toxicity (halofantrine).

For drugs with a narrow therapeutic index and the need for dose titration (such as hydralazine, tacrolimus and carbamazepine), even small changes in dose-response effects can have great consequences. In susceptible patients, even moderate food-drug interactions may cause dosage difficulties for such drugs, and drug administration with a consistent relation to food intake should be considered.

Awareness of food-drug interactions may also help to improve patients' compliance with some drugs, e.g. administration of erythromycin and NSAIDs with food reduces adverse symptoms that may otherwise lead to noncompliance.

Several cases (mainly in the US) of drug-grapefruit juice interactions have now been described, and interactions have also been shown in studies after extensive intake of concentrated grapefruit juice. These interactions can be very pronounced and involve the development of severe adverse effects and even death. However, in most countries the daily intake of grapefruit juice is moderate or small and the occurrence of clinically significant grapefruit juice–drug interactions is likely to be very rare. Accordingly, grapefruit juice–drug interactions have not been included in table I.

This review gives guiding recommendations for administration of drugs with significant food-drug interactions. However, we are well aware that a number of other factors in individual patients can influence their sensitivity to food-drug interactions. Dietary habits, specific diseases, polypharmacy, compliance and enzyme constitution can all affect a patient's potential for developing interactions with food, and dosage adjustments need to be individualised. Thus, the physician needs to be aware of potential food-drug interactions in order to assess whether they are relevant in the treatment of a specific patient.

Increasing quality demands in healthcare necessitate the formulation of strategies to identify and prevent food-drug interactions.[1] In hospitals, it is important that not only physicians but also the nursing staff are aware of food-drug interactions, since nurses administer both drugs and food. Educational programmes or standard operating procedures should be available in hospital departments. When discharged from hospital, the patients should be given information, orally as well as written, of potential food-drug interactions. Also, general practitioners, pharmacists and district nurses require a continuously updated knowledge of food-drug interactions, as they are key people for providing the non-hospitalised patient with information on relevant food-drug interactions.

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