CONTINUING MEDICAL EDUCATION

Drug Interactions—Principles, Examples and Clinical Consequences

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SUMMARY

Background: Drug interactions can have desired, reduced or unwanted effects. The probability of interactions increases with the number of drugs taken. The high rate of prescribed drugs in elderly patients (65-year-old patients take an average of 5 drugs) increases the likelihood of drug interactions and thus the risk that drugs themselves can be the cause of hospitalization. According to meta-analyses, up to 7% of hospitalizations are drug-related.

Methods: Selective literature review.

Results: Drug interactions occur on pharmacodynamic and pharmacokinetic levels. Examples of pharmacodynamic interactions are simultaneous administration of a NSAID and phenprocoumon (additive interaction), or of aspirin and ibuprofen (antagonistic interaction). Pharmacokinetic interactions occur at the levels of absorption (e.g., levothyroxine and neutralizing antacids), elimination (e.g., digoxin and macrolides), and metabolism, as in the competition for cytochrome P450 enzymes (e.g., SSRIs and certain beta-blockers).

Conclusion: The systematic knowledge of drug interaction, in particular on the level of absorption, elimination, transport and drug metabolism may help to prevent adverse effects. Predicting pharmacodynamic interactions often demands a deeper understanding of the mechanisms of effect. Electronic prescribing systems are helpful.

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Increasing multimorbidity with age often makes it necessary to prescribe several drugs for one patient at a time. As a consequence, the average 65-year-old patient is on five drugs simultaneously (1). Prescription peaks in the 75- to 84-year-old group; a European study showed among patients with a mean age of 81 years that 34% to 68% were taking six drugs or more (2).

A necessary consequence of this is the danger that interactions between drugs will lead to serious adverse effects or will reduce the therapeutic effect of some compounds. Potential interactions can arise at any age in life, but the frequency of polypharmacy in older life increases the risk substantially. Meta-analyses of the reasons for inpatient admission to medical wards showed that in 7% of cases serious drug interactions were the cause for admission or for prolonged hospital stays (3, e1, e2). Similar conclusions were reached in an earlier Austrian study of 543 newly admitted elderly patients (median age: 82 years), who were taking 7.5 ± 3.8 drugs at the time of their admission (4). The authors regarded 36% of the drugs as unnecessary and 30% as inappropriate for elderly people (see recommendations in the PRISCUS list [5]). For 10% of the patients, adverse drug effects were regarded as the reason for their inpatient admission, and in 18.7% a drug interaction very probably played a part in these effects (6). Adverse drug effects are also a—sometimes avoidable—problem during inpatient treatment. One of the frequent causes here is incorrect or wrongly adjusted dosages, especially in patients with reduced kidney function (7). A British study of 3695 patients demonstrated that almost 15% of the patients suffered adverse drug effects during their stay in hospital, which in a quarter of these cases prolonged the hospital stay. Once sex, age, and type of ward (medical, surgical) were taken into account, the number of simultaneously prescribed drugs was the only significant predictor (7). In a survey in

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Drug interactions

Interactions between drugs can lead to serious unwanted effects or to a reduction in the therapeutic effects of some drug substances. Polypharmacy, which is common in elderly patients, increases the risk substantially.

Sweden, the contribution of drugs to overall mortality was estimated at 3%; gastrointestinal and central nervous bleeding alone contributed a third of the incidence (e3).

Knowing about interactions and their causes may help to avoid them. One study, in which hospital personnel on an intensive care unit were informed of drug interactions by written drug information based on a computerized clinical decision support system, was very successful, reducing the number of interactions from 66% to 54% and the number of unwanted events from 44% to 25% (e4) (*Box 1*).

BOX 1

Causes of unwanted drug effects and interactions

- Wrong choice of drug
- Failing to take account of renal function
- Wrong dosage
- Wrong route of administration
- Errors in taking the drug
- Transmission errors

Learning goals

This CME article gives examples of interactions at the pharmacodynamic level, mainly using the example of nonsteroidal anti-inflammatory drugs (NSAIDs). The focus is on demonstrating the systematics of pharmacokinetic interactions. The learning goals follow from this: knowledge of important and frequent

- pharmacodynamic interactions
- pharmacokinetic interactions at the absorption and excretion levels, and
- pharmacokinetic interactions at the drug metabolism level, chiefly of cytochrome P450 enzymes

The review article is based on a selective literature search in PubMed and publicly accessible databases such as http://medicine.iupui.edu/clinpharm/ddis/. The clinical manifestation of interactions can vary greatly. Inadequate lowering of blood pressure and a blood pressure drop that may be so extreme as to cause hypovolemic shock can both result from pharmacodynamic and/or pharmacokinetic interactions. To avoid serious consequences so far as possible from the outset, therefore, requires the ability to make better predictions about drug interactions. In some cases, however, desired interactions can improve the therapeutic effect, e.g., if local bioavailability is increased by inhibition of the metabolic pathways.

Pharmacodynamic interactions

The term "pharmacodynamic interactions" refers to interactions in which drugs influence each other's effects directly. As a rule, for example, sedatives can potentiate each other. The same is true of alcohol, which can potentiate the sedative effects of many drugs.

Often, however, a pharmacodynamic interaction is actually desired, if mutually potentiating effects in the same direction (synergistic effects) are aimed at, e.g., in the use of anti-infectives or in pain therapy. When the effect of one drug is impeded by another, the effects of these drugs are antagonistic.

Even barely observable undesired effects can potentiate each other in a dangerous manner. For example, if fluoroquinolones are combined with macrolides such as erythromycin, this can result in QT prolongation. The combination of ACE inhibitors with potassium-sparing diuretics such as amiloride can increase potassium retention so strongly that life-threatening hyperkalemia ensues. Interactions of nonsteroidal anti-inflammatory drugs (NSAIDs) are demonstrated below as an example of pharmacodynamic interactions.

Pharmacodynamic interactions of NSAIDs

Platelet-related interactions—It is generally known that simultaneous administration of NSAIDs increases the COX-1-mediated inhibition of thromboxane synthesis and hence the risk of gastrointestinal bleeding in a synergistic manner. A particular property of the acidic anti-inflammatory ibuprofen is its specific, reversible binding to COX-1, which prevents acetylsalicylic acid (ASA) from acetylating the serine residue at position 529 of the COX-1 protein. Irreversible and hence long-lasting inhibition of COX-1-mediated thromboxane A_2 synthesis by ASA can thus be prevented and the cardiac risk of patients with coronary heart disease can increase (8).

Long-term clinical observations confirm these *ex vivo* observations (e5), which appear also to hold for naproxen (e6). Accordingly, patients with coronary heart disease on ASA prophylaxis should not take ibuprofen or naproxen on a regular basis.

Pharmacodynamic interaction

Pharmacodynamic interactions are those in which drugs influence each other's effects directly.

Increased potassium retention

The combination of ACE inhibitors and potassium-sparing diuretics such as amiloride can increase potassium retention so strongly that life-threatening hyperkalemia ensues.

TABLE 1

Examples of typical additive and antagonistic pharmacodynamic interactions

Substance I	Substance II	Possible effect
Additive interactions		
NSAIDs	SSRI, phenprocoumon	Increased risk of bleeding
NSAIDs	Glucocorticoids	Increased risk of gastric bleeding
ACE inhibitors	Spironolactone, amiloride	Hyperkalemia
SSRIs	Triptans	Serotonin syndrome
Tricyclic antidepressants	Low-potency neuroleptics	Increased anticholinergic effects
Quinolones	Macrolides, citalopram	QT-interval prolongation, torsade de pointes
Antagonistic interactions		
Acetylsalicylic acid	Ibuprofen	Reduced effects
ACE inhibitors	NSAIDs	Reduced effects
Levodopa	Classical neuroleptics	Reduced effects
Phenprocoumon	Vitamin K	Reduced effects

SSRI, selective serotonin reuptake inhibitor; NSAID, nonsteroidal anti-inflammatory drug

Increased gastrointestinal bleeding also occurs when selective serotonin reuptake inhibitors (SSRIs) such as citalopram are taken simultaneously with NSAIDs (e7). SSRIs inhibit the transport of serotonin into the platelets, leading to further impairment of function and doubling of the risk of bleeding. The SSRI-mediated impairment of platelet function can also increase the risk of bleeding due to vitamin K antagonists such as warfarin and phenprocoumon (9, e8). SSRIs were associated with an increased risk of gastrointestinal bleeding with an odds ratio of 2.6 (95% confidence interval [CI] 1.5 to 4.3), whereas other antidepressants barely increase the risk. NSAIDs and specific COX-2 inhibitors, on the other hand, also increased the risk of bleeding, with an odds ratio of 2.6 (95% CI 1.6 to 4.2) and 3.1 (95% CI 1.4 to 6.7), respectively. These study results thus indicate that SSRIs increase the risk of bleeding associated with vitamin K antagonists as much as NSAIDs do. Since the absolute number of bleeding events under SSRI treatment is quite low, however, simultaneous treatment with SSRIs and anticoagulants or NSAIDs should chiefly be avoided in at-risk patients with a known history of bleeding (e7).

Interactions with the vascular system—NSAIDs can reduce the blood-pressure-lowering effect of ACE inhibitors. The main mechanism is via a reduction in glomerular perfusion through a reduction of local prostaglandin E_2 synthesis with corresponding reactive secretion of renin. In a controlled clinical study, the blood pressure of healthy volunteers treated with lisinopril rose by 7 to 9 mmHg when they were given piroxicam (e9). It was recently reported that these important interactions of NSAIDs are also true for AT1-receptor blockers (10). Low-dose ASA, on the other hand, appears to have no effect on arterial blood pressure (e10). Nevertheless, doses of 300 mg ASA and higher can reduce the effects of ACE inhibitors.

Other interactions of inhibitors of the renin–angiotensin system (RAAS)—The aldosterone-antagonistic effect of ACE inhibitors and AT1-receptor antagonists can, in combination with potassium-sparing diuretics or specific aldosterone antagonists such as spironolactone and eplerenone, induce dangerous hyperkalemia or renal failure. After the introduction of spironolactone for the treatment of cardiac failure, the number of hospitalizations for hyperkalemia increased markedly (11). Apparently there now exists an increased awareness of this potential problem, however; although, according to the guidelines of the European Society of Cardiology (ESC), aldosterone antagonists are the drug of choice for patients with NYHA class II heart failure, alongside RAAS inhibitors, and consequently are being used more widely, more recent studies do not show significant hyperkalemia when they are used in combination with RAAS inhibitors (e11, e12).

With pharmacodynamic interactions, it is not possible to demonstrate a simple systematics as it is in pharmacokinetic interactions; instead, they require a careful weighing up of which drug groups cause desired and which undesired effects, which can in turn either potentiate or weaken each other (*Table 1*).

Pharmacokinetic interactions

Reciprocal influencing of absorption, distribution in the various compartments, metabolization, and elimination can affect the effective concentrations at their sites of action. The causes can be formation of complexes, competition for uptake transporters, or induction of metabolizing enzymes and efflux transporters (*Figure 1*).

Cardiac risk

Patients with coronary heart disease who are taking prophylactic ASA should not at the same time be given ibuprofen or naproxen.

Renin-angiotensin system inhibitors

The antihypertensive effect of ACE inhibitors can be weakened by NSAIDs.

The systematics are becoming increasingly better understood, so that some of the interactions of various drugs can be well predicted, partly with the help of computer programs, at least for certain drug groups (12). Quantification of the extent of the interaction, however, is not usually subject to any simple rule, such as in dose adjustment of renally eliminated drugs depending on the patient's glomerular filtration rate.

Interactions at the absorption level—formation of complexes

Complexes can considerably reduce the bioavailability of drugs. The bisphosphonates used in osteoporosis, such as alendronate, have a very low bioavailability of only 0.5% to 2%. Calcium ions in mineral water or milk reduce this markedly still further. Multivalent cations can also form complexes with tetracycline or quinolones and also reduce the bioavailability of levothyroxine; simultaneous intake of calcium-containing foods or neutralizing antacids containing aluminum or magnesium ions, must therefore be avoided. Recently, a reduction of the protective properties of alendronate with reference to avoiding hip fractures was observed when proton pump inhibitors were given at the same time (13).

Interactions at the absorption level—membrane transport

Multidrug efflux transporters such as P-glycoprotein (P-gp, ABCB1) were first described as one of the causes of chemotherapy resistance in tumors. P-glycoprotein is expressed in many tissue barriers such as intestine, liver, kidney, and blood–brain barrier, and in the placenta, testis, lymphocytes, and tumor cells, and extrudes predominantly lipophilic connections/bindings from inside the cell via the apical membranes of epithelial or endothelial cells.

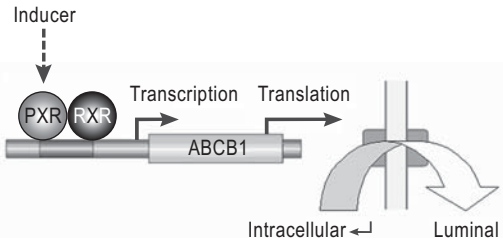
Inhibition of this efflux transporter could therefore help to overcome chemoresistance. P-gp-mediated efflux transport also contributes to reducing the responsiveness of lymphocytes to HIV protease inhibitors. Ritonavir, which causes many side effects at high doses, simultaneously inhibits P-gp and also the drug-metabolizing cytochrome P450 3A4 (CYP3A4). The fixed combination of ritonavir with, for example, 200 mg lopinavir improves the bioavailability of the protease-inhibiting substance and the efflux of lopinavir out of the lymphocytes, thus reducing the breakdown in the liver. So far, however, the attempt to overcome the chemoresistance of tumors by inhibiting efflux transporters, especially by means of P-glycoprotein, has been unsuccessful.

BOX 2

Levels of pharmacokinetic interactions (ADME principle)

- **A**bsorption in the bowel
- **D**istribution (crossing between compartments, e.g., across blood–brain barrier, plasma protein interactions)
- **M**etabolization (liver and bowel)
- **E**limination (kidneys)

FIGURE 1



Example of induction: P-glycoprotein, the most important efflux transporter at several interfaces can be induced by rifampicin. PXR, pregnane X receptor; RXR, retinoid X receptor

An example of a typical drug interaction at the P-gp level is the much higher bioavailability of the cardiac glycoside digoxin when accompanied by oral administration of the calcium antagonist verapamil.

A selection of P-gp substrates, inhibitors, and inducers is shown in *Table 2*.

P-gp induction can, on the other hand, accelerate efflux transport and reduce the bioavailability of drugs. For ciclosporin, this means that simultaneous administration of the tuberculostatic rifampicin can lead to subtherapeutic concentrations. Rifampicin binds intracellularly to the nuclear receptor PXR, one of the main regulators of transcriptional control of P-gp expression (14, e13) (*Figure 2*). Other PXR ligands,

Aldosterone antagonists

Aldosterone antagonists taken in combination with RAAS inhibitors can cause hyperkalemia. Renal function must be taken into account.

Bisphosphonate absorption

The bisphosphonates, used in osteoporosis such as alendronate, have a very low bioavailability of only 0.5% to 2%. Calcium ions in mineral water or milk sharply reduce this still further.

TABLE 2

Examples of interactions at the intestinal absorption level: selection of relevant substrates, inducers, and inhibitors of P-glycoprotein (ABCB1)

Group	Substance
Substrates	
Opioids	Loperamide, morphine
Antihypertensives	Aliskiren, carvedilol
Anticoagulants	Dabigatran
Cardiac glycosides	Digoxin
Immunosuppressants	Ciclosporin, tacrolimus, sirolimus
Protease inhibitors	Indinavir, saquinavir
Statins	Atorvastatin, lovastatin, simvastatin
Antineoplastic agents	Paclitaxel, anthracyclines, vinca alkaloids, etoposide, imatinib
Inducers	
Anticonvulsants	Carbamazepine (oxcarbazepine less so), phenytoin, phenobarbital, primidone
Tuberculostatics	Rifampicin
Antiretroviral	Efavirenz
St. John's wort extract	Hyperforin
Inhibitors	
Antimycotics	Itraconazole, ketoconazole
Calcium channel blockers	Diltiazem; felodipine; nicardipine; nifedipine; verapamil especially
Macrolide antibiotics	Erythromycin, clarithromycin, not azithromycin
HIV protease inhibitors	Indinavir; nelfinavir; ritonavir especially; saquinavir
Immunosuppressants	Ciclosporin
Antiarrhythmic drugs	Amiodarone, quinidine, propafenone

and thus inducing drugs, are the anticonvulsants carbamazepine (oxcarbazepine to a lesser extent), phenobarbital, and phenytoin, and the HIV therapeutic efavirenz. A case of unexpected clinical significance was one where ingestion of St. John's wort extract led to such a pronounced fall in ciclosporin concentration that an acute transplant rejection occurred (15). The substance responsible for this was hyperforin, which is present in St. John's wort extract and was identified as another PXR ligand.

In addition to P-gp, the efflux transporters ABCC2 (MRP2) and ABCG2 (BCRP) are also responsible for the efflux transport of many medical drugs and can be subject to interactions with inhibitors.

The opposite also occurs: inhibition of uptake transporters leads to a reduction in bioavailability. An example is inhibition by repaglinide of the uptake of metformin via the organic cation transporter OCT1 (e14).

Interactions at the metabolic level

Inhibition of drug metabolism is a frequent cause of drug interactions. Most metabolic interactions are due to competition for the cytochrome P450 enzyme (CYP), which is expressed in the liver and catalyzes the phase I oxidation of more than half of all medical drugs (16).

Interactions with CYP3A4 are particularly marked, since this isoenzyme has a particularly broad substrate spectrum (e15). Some of the CYP3A4 substrates, inhibitors, and inducers are identical with those of P-gp, indicating a synergistic defense mechanism against foreign matter that has developed in the course of evolution (*Tables 3 and 4*).

Anticoagulants—The most relevant interactions are those relating to drugs with a narrow therapeutic spectrum, such as ciclosporin or phenprocoumon. As already mentioned, vitamin K antagonists can trigger life-threatening hemorrhage and contribute to the incidence of medical drug-related hospitalizations. The cause could be interactions with older macrolide antibiotics such as erythromycin and clarithromycin, which inhibit cytochrome P450 3A4, important in the metabolization of phenprocoumon. Azithromycin shows almost no interactions with the cytochrome P450 system. The calcium channel blockers verapamil and azole antimycotics can be highly potent CYP3A4 inhibitors. Ketoconazole inhibits the cytochrome P450 system so strongly that it is now used as a standard inhibitor in the clinical development of medical drugs, in order to test interactions with CYP3A4 among others. Fluconazole is another CYP3A4 inhibitor, although a weaker one. Bleeding complications during treatment with fluconazole among others have also been reported in patients on warfarin anticoagulation therapy. In this case, the increased bioavailability of warfarin is due to fluconazole-mediated inhibition of CYP2C9 (e16).

For vitamin K antagonists, however, coadministration of broad-spectrum antibiotics such as amoxicil-

Example of increased bioavailability through inhibition of P-glycoprotein

- Central inhibition by loperamide after administration of verapamil

Example of reduced bioavailability through induction of P-glycoprotein

- Inefficacy of digoxin after coadministration of carbamazepine

lin (alone or with clavulanic acid) or doxycycline appears to be a determinant of bleeding events. The cause is less inhibition of the metabolism, more possibly a change in coagulation status given the underlying pyretic infection (17). This case must be carefully distinguished from a drug interaction.

The flavonoid naringin, contained in citrus fruits (especially grapefruit), also inhibits CYP3A4 and thus can increase the availability of a number of other drugs. In a study carried out in healthy volunteers, the bioavailability of orally administered midazolam did not return to normal until 3 days after the subjects drank one glass of grapefruit juice (e17). The clinical relevance of phenprocoumon is debated, but, at the least, excessive amounts of citrus fruits should be avoided in patients receiving anticoagulation treatment with vitamin K antagonists.

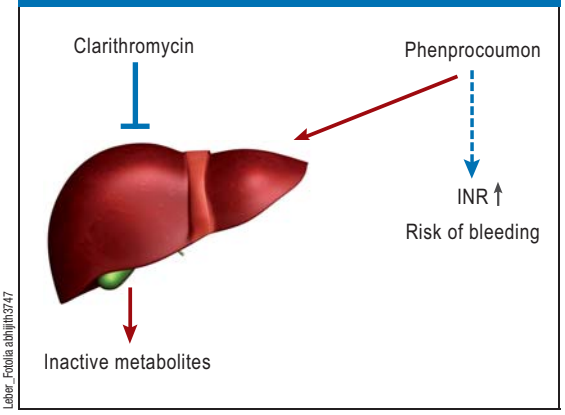
Antidepressants—Selective serotonin reuptake inhibitors (SSRIs) are potent inhibitors of CYP2D6 (fluoxetine, paroxetine) (e18) and CYP1A2 (fluvoxamine). This has consequences for the coadministration of other drugs. In everyday practice, however, one must also watch out for interactions between antidepressants and common medical drugs such as certain beta-blockers. Fluoxetine and paroxetine also inhibit the metabolism of the beta-blocker metoprolol and can thus cause lowering of blood pressure, bradycardia, and other undesired effects.

Fluvoxamine, on the other hand, inhibits CYP1A2 and can thus increase the toxicity of theophylline or clozapine. A fatal interaction between fluoxetine and clozapine has also been reported (e19).

The inhibition of CYP2D6 can also reduce the formation of active metabolites of codeine into morphine or tramadol into *O*-desmethyltramadol. It has been shown in large studies that the inhibition of CYP2D6-mediated activation of the anti-estrogen tamoxifen to endoxifen through SSRIs is associated with increased breast cancer mortality (18).

Apart from the pharmacokinetic interactions, another aspect to consider with SSRIs is potentiation of the serotonergic effects. It is known that simultaneous administration of moclobemide can trigger serotonin syndrome and is contraindicated for that reason. However, other drugs with serotonergic effects such as tramadol or triptans can increase the risk of serotonin syndrome. When triptans such as sumatriptan are used at the same time, there is an additional risk of coronary artery constriction and hypertension.

FIGURE 2



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Inhibition of CYP34A-catalyzed metabolization of the vitamin K antagonist phenprocoumon by the macrolide antibiotic clarithromycin. The result is an increase in bioavailability, in turn increasing the risk of bleeding

Interaction must be expected for several days after the last administration of SSRIs, because of their long half-life (*Box 3*).

Quinolones—Quinolones such as ofloxacin and ciprofloxacin are primarily inhibitors of CYP1A2, which is also involved in metabolism of theophylline or clozapine. Simultaneous administration of, for example, ciprofloxacin and theophylline can lead to a rise in the plasma concentration of theophylline, with corresponding clinical symptoms of cardiac and gastrointestinal unwanted effects (19). The bioavailability of quinolones themselves can be markedly restricted if they are given at the same time as bivalent or trivalent cations, such as are contained in antacids or zinc or iron formulations (*Box 4*).

Proton pump inhibitors (PPIs)—Proton pump inhibitors such as omeprazole, lansoprazole, pantoprazole, or rabeprazole inhibit cytochrome P450 2C19 (CYP2C19) to varying degrees. Omeprazole in particular (esomeprazole less so) is a substrate and inhibitor of CYP2C19. Recently, a discussion has arisen about the consequences of its interaction with the platelet aggregation inhibitor clopidogrel. Clopidogrel is a prodrug that is metabolized to its active metabolites in two steps, and CYP2C19 plays an essential part in this. Ho et al. showed a rise from 20.8% to 29.8% in the rate of deaths or rehospitalization of patients being treated with clopidogrel for acute coronary syndrome and simultaneously with PPIs (adjusted odds ratio 1.25 [95% CI, 1.11 to 1.41]) (20). A similar association was found in carriers of the nonactive genetic variants of

Vitamin K antagonists

Vitamin K antagonists can trigger life-threatening hemorrhage and are one cause of medical drug-related admissions to hospital.

Inhibitor in citrus fruits

The flavonoid naringin, contained in citrus fruits (especially grapefruit), is an inhibitor of CYP3A4 and can increase the bioavailability of many drugs.

TABLE 3

Interactions at the cytochrome P450 enzyme level: selection of relevant substrates for which, when used in combination with inhibitors or inducers of the same enzyme, either increased effects and increased occurrence of unwanted effects, or reduced effects or loss of effect must be anticipated (modified from [24])

CYP1A2	CYP2C9	CYP2C19	CYP2D6	CYP3A4/5	
Clozapine Imipramine Mexiletine Naproxen Tacrine Theophylline	**NSAIDs** Celecoxib Diclofenac Ibuprofen Naproxen Piroxicam **Antidiabetics** Glipizide Tolbutamide **Angiotensin receptor blockers** Irbesartan Lorsartan **Miscellaneous** Cyclophosphamide Fluvastatin Phenytoin Sulfamethoxazole Torasemide Warfarin	**Proton pump inhibitors** Omeprazole Lansoprazole **Miscellaneous** Amitriptyline Clomipramine Clopidogrel* Cyclophosphamide* Diazepam Phenytoin	**Beta-blockers** Metoprolol Propafenon Timolol **Antidepressants** Amitriptyline Clomipramine Desipramine Duloxetin Imipramine Paroxetine Venlafaxine **Antipsychotics** Aripiprazole Haloperidol Risperidone Thioridazine **Opioids** Codeine* Dextromethorphan Tramadol* **Miscellaneous** Ondansetron Tamoxifen*	**Macrolide antibiotics** Clarithromycin Erythromycin **Benzodiazepines** Alprazolam Diazepam Midazolam Triazolam **Calcium channel blockers** Amlodipine Diltiazem Felodipine Nifedipine Nisoldipine Nitrendipine Verapamil **Immunosuppressants** Ciclosporin Tacrolimus Sirolimus **HIV protease inhibitors** Indinavir Ritonavir Saquinavir	**Statins** Atorvastatin Lovastatin Simvastatin **Anticoagulants** Apixaban Rivaroxaban Phenprocoumon **Miscellaneous** Aripiprazole Buspirone Quinidine Quinine Ethinylestradiol Imatinib Sildenafil Tamoxifen Vincristine

* Prodrug

CYP2C19 (21, e20). Both the *CYP2C19*2*-splice-site variant and the *3 missense variant lead to a complete loss of effect of the protein. Among white people, 3% are homozygote *CYP2C19*2* carriers, while **3* carriers contribute to the "poor metabolizer" status of people of Asian origin. A systematic meta-analysis of follow-up studies confirmed the association between *CYP2C19* polymorphisms and platelet inhibition by clopidogrel, but clinically no significant effect on the risk of cardiovascular events was shown (22). The US Food and Drug Administration (FDA) points out in the safety information on clopidogrel that the drug will have reduced effectiveness in CYP2C19 nonmetabolizers. With regard to interactions, the FDA recommends choosing the proton pump inhibitor pantoprazole rather than omeprazole, if possible. The German drug information, without mentioning any drugs by name, advises against the simultaneous use of strong CYP2C19 inhibitors.

Conversely, omeprazole can inhibit the breakdown of other drugs. An example is citalopram, the metabolization of which is slowed down by omeprazole (e21), and the risk of unwanted effects such as QT prolongation rises. Omeprazole also inhibits demethylation of the benzodiazepine diazepam. At a dose of 20 mg, omeprazole results in a 36% increase in the half-life of diazepam and a 27% reduction in its clearance; giving 40 mg omeprazole increases the half-life by 130% and clearance by 54%. Lansoprazole also inhibits the metabolization of diazepam, although more weakly; this evidence did not appear for pantoprazole (e22).

SSRIs and moclobemide

Simultaneous use of moclobemide and SSRIs can trigger serotonin syndrome and is therefore contraindicated.

Quinolones

Simultaneous use of, for example, ciprofloxacin and theophylline, can lead to a rise in plasma theophylline concentration, with corresponding cardiac and gastrointestinal adverse effects.

TABLE 4

Interactions with the most important cytochrome P450 enzymes: inhibitors and inducers (modified from [25])

CYP1A2	CYP2C9	CYP2C19	CYP2D6	CYP3A4/5
Inhibitors				
Fluoroquinolones Ciprofloxacin ++ Ofloxacin Levofloxacin **Miscellaneous** Amiodarone Cimetidine + Fluvoxamine ++ Ticlopidine	Amiodarone + Fluconazole ++ Isoniazide	**SSRIs** Fluoxetine Fluvoxamine **PPIs** Lansoprazole + Omeprazole + **Miscellaneous** Ketoconazole Ticlopidine	**SSRIs** Duloxetin + Fluoxetine ++ Paroxetine ++ **Miscellaneous** Amiodarone Buproprion Cimetidine Quinidine ++ Chlorphenamine Clomipramine Ritonavir	**HIV protease inhibitors** Indinavir ++ Nelfinavir ++ Ritonavir ++ **Macrolides** Clarithromycin ++ Erythromycin + **Azole antimycotics** Fluconazole + Itraconazole + Ketoconazole ++ Voriconazole **Miscellaneous** Aprepitant +, Amiodarone Cimetidine + Diltiazem Naringin + (in citrus fruits) Verapamil +
Inducers				
Tobacco smoke Omeprazole	Rifampicin			Carbamazepine (oxcarbazepine less so) Efavirenz Hyperforin (in St. John's wort) Phenobarbital Phenytoin Rifampicin

++, strong inhibition; +, intermediate inhibiton; no +, weak or undefined inhibition

In addition to inhibiting CYP2C19, omeprazole leads to reduced induction of CYP1A2 (23, e23).

While lansoprazole is also able to induce CYP1A2, this interaction was not observed with pantoprazole (24). Pantoprazole appears to show almost no interactions.

A significant influence of omeprazole on the bioavailability of the HIV protease inhibitor atazanivir was observed, not mediated by cytochrome P450, but as a consequence of the rise in pH. In volunteers receiving 300 mg atazanivir/100 mg ritonavir for 2 weeks, a reduction in atazanivir C_{max} by 48% and of the AUC by 62% was observed during treatment with 40 mg omeprazole and also during treatment with 150 mg ranitidine. The kinetics of lopinavir were not changed by omeprazole or ranitidine (e24). According to the safety information, increasing the atazanivir dose to 400 mg does not compensate for the impact of omeprazole on atazanivir exposure. For this reason, neither PPIs nor, presumably, H_2-receptor blockers should be used simultaneously with atazanivir.

Conclusions

Pharmacokinetic interactions in particular are systematic. Knowledge of which enzymatic metabolic path is clinically relevant to the metabolization of a drug, whether it is the substrate of a drug transporter, and whether it inhibits or induces these proteins, makes it possible to predict pharmacokinetic interactions. Inhibitors of certain cytochrome P450 enzymes can in-

Proton pump inhibitors

Proton pump inhibitors such as omeprazole, lansoprazole, pantoprazole, and rabeprazole inhibit cytochrome P450 2C19 (CYP2C19) to varying degrees.

Omeprazole and clopidogrel

Both these drugs have a low response rate in CYP2C19 nonmetabolizers. With regard to interactions, the FDA recommends choosing not omeprazole but pantoprazole if possible.

BOX 3

Clinical examples of the change in bioavailability of the cytochrome P450 enzymes

- **Bioavailability can be increased by inhibition of cytochrome P450 enzymes**
  - Risk of renal toxicity with ciclosporin if clarithromycin is given
  - Risk of bleeding if verapamil is given to patients on phenprocoumon anticoagulation therapy
  - Myalgia due to simvastatin if fluconazole is also given
  - Increase in theophylline toxicity if ciprofloxacin is given
- **Bioavailability can be reduced by induction of cytochrome P450 enzymes**
  - Transplant rejection in patients on ciclosporin for immune suppression who are comedicated with rifampicin
  - Thrombosis risk in patients on phenprocoumon anticoagulation therapy who are comedicated with carbamazepine
  - Efficacy of ethinylestradiol contraceptives is at risk if efavirenz is given at the same time.

fluence the bioavailability of a whole group of drugs metabolized by the same enzyme, while inducers usually contribute to a loss of effectiveness. As a general principle, drugs that are metabolized more quickly and have a lower bioavailability carry a higher potential risk of interactions. Predicting pharmacodynamic interactions often requires a deeper understanding of the mechanisms of action; but here too a certain system can be recognized, just as for pharmacokinetic interactions. Electronic prescribing systems that can alert the user early on to possible interactions and can assist with drug selection and dosage are helpful.

BOX 4

Quinolone interactions

- Inhibition of cytochrome P450 1A2 by quinolones (principally pefloxacin and ciprofloxacin, less by ofloxacin, levofloxacin, or moxifloxacin)
- Combination with NSAIDs (except for aspirin) increases tendency to seizures
- Combination with macrolides (prolongation of QT interval with risk of malignant cardiac arrhythmias such as torsade de pointes)

Conflict of interest statement
Professor Cascorbi has received fees for preparing medical educational events from Novartis, MSD, and Sanofi-Aventis.

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Potential risk

As a general principle, drugs that are metabolized more quickly and have a lower bioavailability carry a higher potential risk of interactions.

Future prospects

Electronic prescribing systems that can alert the user early on to possible interactions and can assist with drug selection and dosage are helpful.

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Günther P, Rübben I: The Acute Scrotum in Childhood and Adolescence.

Answers: 1b, 2a, 3e, 4e, 5c, 6b, 7a, 8c, 9a, 10b

Please answer the following questions to participate in our certified Continuing Medical Education program. Only one answer is possible per question. Please select the answer that is most appropriate.

Question 1

Which drug can increase the platelet inhibiting effect of NSAIDs?

a) Erythromycin
b) Mirtazapine
c) Citalopram
d) Rifampicin
e) Fluconazole

Question 2

The antihypertensive effect of ACE inhibitors can be specifically reduced by inhibition of renal prostaglandin synthesis. Which of the following drugs interacts in this process?

a) Low-dose ASA
b) Hydrochlorothiazide
c) Verapamil
d) Diclofenac
e) Morphine

Question 3

ASA inhibits platelet aggregation. Which analgesic can reduce this effect if given at the same time?

a) Ibuprofen
b) Diclofenac
c) Meloxicam
d) Paracetamol
e) Etoricoxib

Question 4

Which drug increases the bioavailability of digoxin by inhibiting the P-glycoprotein efflux transporter?

a) Dabigatran
b) Hypericin
c) Rifampicin
d) Clarithromycin
e) Morphine

Question 5

Which drugs, if taken at the same time, increase the risk of gastrointestinal bleeding due to an additive interaction?

a) Paracetamol + triptan
b) Phenprocoumon + NSAID
c) SSRI + paracetamol
d) Quinolone + warfarin
e) Macrolide + NSAID

Question 6

A patient who has received a renal transplant is on ciclosporin therapy. He says he has been feeling down recently and is therefore taking St. John's wort. What could be one effect of the comedication?

a) Increased coagulation time
b) Increased ciclosporin toxicity
c) Hypertrichosis
d) Increased thrombosis risk
e) Transplant rejection

Question 7

A patient who has been taken off the beta-blocker metoprolol is treated with fluoxetine for depression. What unwanted effect should be expected?

a) Bradycardia
b) Skin bleedings
c) Increase in blood pressure
d) Anemia
e) Hyperglycemia

Question 8

What is the name of the flavonoid contained in citrus fruits that is an inhibitor of CYP3A4?

a) Apigenin
b) Naringin
c) Chrysin
d) Luteolin
e) Hesperetin

Question 9

What effect should be expected in a patient taking clopidogrel and omeprazole simultaneously?

a) Omeprazole increases the side effects of clopidogrel
b) Increased risk of thrombotic-thrombocytopenic purpura
c) Omeprazole raises the plasma concentration of the active clopidogrel metabolite
d) Reduction of the clopidogrel-mediated inhibition of platelet aggregation
e) Clopidogrel inhibits the breakdown of omeprazole

Question 10

The term "synergy" is used in pharmacodynamics to describe mutual influencing of the effects of two drugs. What does synergy mean?

a) Mutual strengthening of effect
b) The effect can only be achieved by giving the drugs at the same time
c) An effect that is at least more than the additive effect of both drugs
d) Reduction of the side effects
e) Mutual canceling out (neutralization) of effects

CONTINUING MEDICAL EDUCATION

Drug Interactions—Principles, Examples and Clinical Consequences

Ingolf Cascorbi

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