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Important Drug Interactions in Dermatology

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Abstract

Drug interactions can occur at any step from absorption to elimination of a drug, and can induce adverse as well as beneficial effects. Since systemic drugs are increasingly available and important in the treatment of dermatological diseases, a variety of possible interactions between concomitantly administered drugs have to be considered by dermatologists.

The xenobiotic-metabolising enzyme system cytochrome P450 (CYP) is involved in the metabolism of many drugs, regulating their plasma concentrations and activities. Furthermore, the adverse effects of many drugs depend on the basal activity and inducibility of particular CYP isoenzymes in an individual patient. Since drug therapy in dermatological practice is of increasing complexity, and an increasing number of potent systemic drugs have become commonly used therapeutic agents, this review focuses on the following topics with the aim of optimising dermatological drug therapy.

In the first section, all the different types of drug interactions that can occur through pharmacokinetic and pharmacodynamic mechanisms are introduced briefly, and then discussed systematically with special reference to drugs important for dermatologists. Then, the network of drug interactions that may occur from absorption to elimination is presented. The most important drug interactions mediated by CYP isoenzymes are listed. Finally, the importance of pharmacogenetics for the development of new drugs and its potential impact on the optimisation of individual therapy regimens is discussed.

The increasing availability of systemic drugs for the treatment of skin diseases is reflected by an increasing necessity to consider adverse drug reactions caused by drug interactions. Such pharmacologically relevant drug interactions can occur at any step from absorption to elimination.[1,2] Drug interactions occurring before absorption, such as precipitations caused by an incorrect mixture of several drugs, are termed drug incompatibilities.

Depending on the individual patient, the prevalence of adverse drug reactions varies from 0.3% to more than 80%, as observed in elderly patients who may take more than 20 different drugs simultaneously.[3,4] Therefore, patients receiving multiple drugs, such as those with AIDS, diabetes mellitus or other chronic diseases, are at very high risk of developing adverse reactions caused by drug interactions.

Drug interactions can induce adverse as well as intended effects. For example, the competition between penicillin and probenecid for renal elimination results in increased penicillin serum concentrations, and in the past was employed as a way to decrease the expense of penicillin therapy. Similarly, it has been suggested to combine cyclosporin with ketoconazole or grapefruit juice,[5] and to increase the efficacy of retinoid therapy by concomitant treatment with inhibitors of retinoic acid 4-hydroxylation such as azole derivatives or vitamin D (colecalciferol) analogues.[6]

Unfortunately, most drug interactions occur in the form of adverse effects. In the use of commercially available drugs, and especially in the development of new drugs, the detection of drug interactions is one of the main challenges in clinical pharmacology.

In the development of new drugs, potential interactions between drugs with low therapeutic indices require careful consideration. Usually, such clinical testing is performed in healthy participants, and the tolerability of a drug in patients with hepatic or renal dysfunction can only be estimated from these data. However, clinical studies in patients with hepatic or renal dysfunction are usually conducted with low numbers of patients. The complexity of these considerations is exemplified by the fact that a constant inhibition of the metabolism of drug A by 50% can be less problematic with regard to the maintenance of a stable therapeutic concentration than an inhibition of 25% that varies from 10 to 70%.[7] Adverse drug interactions occur especially in patients receiving drugs with a low therapeutic index (table I). For most of these drugs, determination of plasma drug concentrations may reduce the risk of potentially hazardous interactions. However, not all of these drugs need to have plasma concentration monitoring during therapy.

Usually, several factors are required for a theoretically predictable interaction to become clinically relevant. A study in 2422 patients over 25 005 days of therapy revealed 113 (4.7%) drug combinations with potential interactions but only 0.3% leading to detectable clinical manifestations,[3] indicating that the recognition of clinically relevant drug interactions remains a challenge for every physician and healthcare professional who is responsible for patients receiving multiple drugs.

Eight different types of 'adverse drug reactions' can be distinguished. In the present review they are termed 'type A' to 'type H' to provide a systematic overview (table II). Here, types B, C, F and H cannot always be predicted before drugs are commercially available and administered. Drug interactions can be further distinguished as pharmacodynamic and pharmacokinetic interactions (table III).

This review will focus on the different potential mechanisms of drug interactions and their clinical significance, with special regard to dermatological

Table I. Drugs with a low therapeutic index

Drug	Adverse effect
Anticonvulsants	CNS toxicity
Antihistamines (terfenadine, astemizole)	Cardiotoxicity, QT-interval prolongation, ventricular arrhythmias
Cyclosporin	Nephrotoxicity, hypertension
Digitalis glycosides	Cardiotoxicity
Methotrexate	Hepatotoxicity, haematological toxicity
Oral anticoagulants	Haemorrhage
Oral contraceptives	Pregnancy, intermenses spotting

Table II. Classification of adverse drug reactions

Type	Description
A	Dose-dependent reaction
B	Idiosyncratic reaction not related to known pharmacological actions, altered relation between dose and effect, strong interindividual variation
C	Alteration of efficacy during long term treatment (tachyphylaxis)
D	Late onset (teratogenicity and carcinogenicity)
E	Overdosage or accumulation/distribution from binding sites
F	Drug interactions (pharmacokinetic or pharmacodynamic)

pharmacotherapy and the drugs most commonly used in this area. Furthermore, the cytochrome P450 (CYP) isoenzyme system is given special consideration since it is involved in the metabolism and the interactions of various drugs commonly used in dermatological practice. An understanding of the metabolic pathways of these drugs makes their interactions and/or adverse effects more comprehensible.

1. Pharmacodynamic Interactions

Drug interactions related to the specific pharmacological effects of administered drugs are termed pharmacodynamic interactions (table IV). Here, the interaction of retinoids with tetracycline and minocycline is of great concern in dermatology since it can lead to the development of increased intracranial pressure. Other antibacterials such as penicillins, cephalosporins and erythromycin do not show such adverse effects in association with retinoids.[8]

Another hazardous interaction is that of methotrexate, which is frequently used in patients with severe psoriasis, psoriatic arthritis or bullous diseases, with trimethoprim. Both agents inhibit dihydrofolate reductase. Although trimethoprim is active preferentially in bacteria, it can also inhibit the human enzyme. In combination with methotrexate this can cause severe myelosuppression.[3] Therefore, the combination of these two drugs should be strictly avoided.

Since HIV infection is a sexually transmitted disease, and therefore belongs to the field of dermatological practice, dermatologists have recently become more involved in the treatment of HIV infection and related diseases. In HIV-positive patients, for example, the combined use of the antiviral ganciclovir with the nucleoside analogue zidovudine has been reported to cause severe haematological complications.[9]

Hypertensive crises after administration of local anaesthetic agents containing epinephrine (0.025 to 0.04%) in patients treated with β-blockers can develop, but only after administration of relatively high amounts, such as during microsurgery.[8] Furthermore, possible paradoxical effects of epinephrine during treatment of anaphylactic shock in patients receiving β-blockers may require very high doses of epinephrine.[10] Therefore, intracutaneous tests, as well as allergy testing by oral challenge or specific desensitisation therapy (immunotherapy), should not be performed while patients are receiving

Table III. Classification of drug interactions

Type	Example
Pharmacodynamic interactions	
See table IV	
Pharmacokinetic interactions	
Interactions during absorption: pH alterations, gastrointestinal motility, formation of complexes	Calcium salts decrease intestinal absorption of tetracycline
Competitive binding to serum proteins	Sulfonamides displace methotrexate from binding sites
Inhibition/induction of drug-metabolising enzymes (e.g. cytochrome P450)	Azole antifungal agents decrease hepatic metabolism of astemizole and terfenadine
Interactions during drug elimination: alteration of enterohepatic circulation and renal clearance	Salicylates decrease the renal excretion of methotrexate, azole antifungal agents inhibit retinoid catabolism

Table IV. Pharmacodynamic drug interactions

Drug	Interacting drug	Effect
Amitriptyline	Minocycline	Skin pigmentation
Amphotericin (intravenous)	Nucleoside analogues or intravenous pentamidine	Nephrotoxicity
Azathioprine	Allopurinol	Pancytopenia
Azoles	Aciclovir	Potentiated antiviral effects
Cephalosporins (second generation)	Aminoglycosides	Increased nephrotoxicity
Cyclosporin	Colchicine	Severe gastrointestinal-, hepatic-, renal- and neuro-toxicity
Epinephrine	β-Blockers	Hypertensive crisis
Erythromycin	Warfarin	Increased anticoagulation and haemorrhage
Methotrexate	Sulfonamides	Increased methotrexate toxicity
Methotrexate	Trimethoprim	Bone marrow suppression
Retinoids	Tetracycline or minocycline	Pseudotumour cerebri, elevated intracranial pressure

β-blockers. The great clinical importance of this interaction for all dermatologists who perform allergological testing or treatments can not be overemphasised.

Another problem is the induction of photosensitisation and related reactions during dermatological treatment. For instance, in patients receiving psoralen-ultraviolet A (PUVA) therapy, photosensitisers such as astemizole, chlorothiazide, coal tar, griseofulvin, interferon (IFN)α–2β, retinoids (e.g. tretinoin, isotretinoin), methoxsalen, nalidixic acid, naproxen, quinolones (e.g. ciprofloxacin), terfenadine, tetracyclines (e.g. minocycline, doxycycline) and sulfonic derivatives should be administered carefully to prevent such adverse effects. Of course, photosensitisation can be triggered during administration of these drugs not only by phototherapy but also by natural sunlight exposure. Intake of such drugs has to be evaluated very carefully by the dermatologist, especially in patients who are being treated by more than one physician, before starting PUVA or other phototherapy regimens.

2. Pharmacokinetic Interactions

2.1 Absorption

Pharmacokinetic drug interactions can occur at each step between absorption and elimination. Most of the interactions during drug absorption that are of relevance for dermatologists occur between drugs and food components. Milk products containing high amounts of calcium and magnesium form chelated complexes with tetracyclines, quinolones and penicillamine (table V). Similar interactions have been observed between milk products and drugs containing bivalent cations such as antacids. During therapy with gyrase inhibitors, iron supplementation must be avoided.[7]

Drugs with anticholinergic effects, for example some antihistamines (hydroxyzine), inhibit gastrointestinal motility, thereby reducing the rate of intestinal absorption of other drugs.[3] Although the total amount of drug absorbed is not reduced, the retarded resorption of certain drugs (e.g. analgesics) can lead to a critical change in the distribution of a drug between neural and fat tissue and lowered therapeutic concentrations.

Interactions between tetracyclines and digoxin can cause a digitalis intoxication. An alteration of the gastrointestinal milieu caused by tetracyclines is suspected to be the underlying factor for this adverse effect. This type of drug interaction has to be taken into consideration, especially in elderly patients with acneiform skin conditions.

Neomycin evokes a malabsorption syndrome, especially with regard to the absorption of vitamin A (retinol) and, to a lesser extent, penicillin and digitalis glycosides. The underlying pathophysiological mechanism is poorly understood.[3]

Within the family of azoles, some significant differences exist, not only with regard to their anti-

mycotic activity and in the spectrum of drug interactions and adverse effects, but also in their intestinal absorption. The choice of an azole derivative has to be considered by dermatologists for each individual patient. In contrast to ketoconazole and itraconazole, the absorption of fluconazole is unaffected by gastric pH. To increase the solubility and thus the intestinal absorption of ketoconazole and itraconazole, patients are advised to ingest acidic beverages, e.g. lemon and lime carbonated drinks, carbonated water or cola.[11] Drugs increasing gastric pH, such as H_2 antagonists or didanosine, should be taken at least 2 hours after ketoconazole or itraconazole (in combination with acidic beverages), and where possible they should be taken with or after food. This is of great importance for the therapy of AIDS patients with opportunistic *Candida* infections, and for patients with atrophic gastritis or those who have had partial or total gastrectomy.

2.2 Serum Protein Binding

After absorption from the intestine, most drugs bind to serum proteins. The most important serum proteins are albumin and, to a lesser extent, β-globulins and α_1-acid glycoprotein. Here, many drugs may compete for the same binding proteins or alter the tertiary structure, and therefore the binding affinity, of a binding protein. This can lead to increased plasma concentrations of unbound drugs. For example, salicylic acid, a common topical drug for hyperkeratotic skin conditions, can be absorbed percutaneously. Since it exhibits a high binding affinity for albumin, this may increase the plasma concentrations of other drugs bound to albumin. However, in most cases this type of drug interaction has been overestimated in the past.[12] The increase concentration of free drug in the plasma is usually followed by an increased renal or hepatic clearance, resulting in a new 'steady state' of plasma drug concentration that differs to a much smaller extent from previous concentrations than that estimated by *in vitro* testing. This can be explained by the fact that *in vitro* testing reflects only the level of drug interactions, but not the *in vivo* clearance of drugs.

Commonly, drug interactions related to serum protein binding are of greater clinical relevance only under conditions of: (i) low volumes of distribution (e.g. the central compartment blood); (ii) a long elimination half-life; and (iii) a low therapeutic index of a drug (e.g. phenytoin, tolbutamide, anticoagulants).[13]

Table V. Drug interactions during absorption

Drug	Interacting drug	Effect
Amoxicillin	Amiloride	Decreased therapeutic effect of amoxicillin
Antihistamines	Other drugs	Decreased intestinal motility, decreased absorption of other drugs
Azoles	Antacids, H_2 antagonists, didanosine	Lower solubility, decreased plasma azole concentrations
Azoles	Cyclosporin	Increased plasma cyclosporin
Corticosteroids	Cholestyramine	Decreased plasma corticosteroids
Dapsone	Didanosine	Decreased plasma dapsone
Griseofulvin	Barbiturates	Decreased plasma griseofulvin
Penicillamine	Aluminium/magnesium-containing antacids, food, iron-containing drugs	Formation of chelates
Penicillins	Atenolol	Decreased plasma atenolol
Penicillins, vitamin A, digoxin	Neomycin	Neomycin-induced malabsorption syndrome
Quinolones	Aluminium/magnesium-containing antacids, milk, zinc, iron	Formation of complexes of low solubility
Tetracyclines	Aluminium/magnesium-containing antacids, milk, zinc, iron	Formation of chelates with low plasma tetracyclines
Tetracyclines, macrolides	Digoxin	Increased plasma digoxin with cardiotoxicity

Taken together, drug interactions caused by competition for serum protein binding appear to be extremely rare in dermatological practice. However, in patients with albumin deficiency (e.g. liver cirrhosis, renal dysfunction and the elderly), pharmacokinetics and toxicity may be markedly altered, so that even a topical agent such as salicylic acid may cause gastric ulcers or renal toxicity when administered in high amounts.

2.3 Metabolism

A variety of drug interactions at the level of metabolism involve drugs commonly used by dermatologists (table VI). The interactions between cyclosporin and azoles, antihistamines and food components such as naringenin in grapefruit have attracted major interest recently.[5,14] Before we list examples and discuss their impact on clinical therapy, we provide an overview of the enzyme system mainly involved, the CYP isoenzyme superfamily.

Low-molecular-weight xenobiotics and drugs are usually cleaved to hydrophilic metabolites, facilitating biliary and/or renal elimination. This is achieved initially by a CYP isoenzyme, located in the endoplasmic reticulum and containing a porphyrin as a prosthetic group (fig. 1), which produces highly reactive intermediate products. These metabolites are further cleaved to their corresponding organic acids by epoxide hydrases, reductases and transferases.[15] The activity of this enzyme system can be induced or inhibited by various factors such as drugs, dietary constituents, pesticides, tobacco smoking, variable expression of cytokines [e.g. interleukins (IL) 1 and IL-6, IFNγ and tumour necrosis factor α]), and genetic factors.[5,13,16] The liver is the major organ for the CYP system, though extrahepatic tissues are also important, as demonstrated by the CYP3A4-dependent metabolism of cyclosporin in the tissue of the small intestine[15] and the metabolism of retinoids[6] and other xenobiotics in the skin (see Belpaire et al.,[15] and references therein).

CYP isoenzymes are named as follows: the first arabic number indicates the gene family (CYP1), a capital letter names the subfamily (CYP1A) and the last arabic number characterises the individual isoenzyme (CYP1A1). When describing the gene, italics are used (e.g. *CYP1A1*).

For drug and xenobiotic metabolism, 4 families of CYP isoenzymes are the most important in humans; CYP3A4 represents 10 to 60% of hepatic CYP isoenzymes and up to 75% of the CYP isoenzymes in the intestine. In studies addressing interactions of cyclosporin with other drugs, 59 drugs from 17 different classes were found to induce or inhibit CYP3A4.[4] Interindividual variations in

Table VI. Interactions between drugs and xenobiotic-metabolising enzymes

Drug	CYP isoenzyme affected	Effect
Methylcholanthrene, omeprazole, phenobarbital	1A subfamily (induction)	Accelerated cleavage of theophylline
Cimetidine, gyrase inhibitors, tobacco compounds	1A2 (inhibition)	Decreased metabolism of theophylline
Azoles, griseofulvin	2E1 (inhibition)	Disulfiram-like reaction after ethanol ingestion
Ethanol	2E1 (induction)	Increased metabolism of paracetamol (acetaminophen) to hepatotoxic hydroquinone metabolites
Azoles, cimetidine, clarithromycin, erythromycin, indinavir, naringenin, nifedipine, omeprazole, ritonavir, verapamil	3A4 (inhibition)	Decreased metabolism of antihistamines, carbamazepine, caffeine, codeine, corticosteroids, cyclosporin, dapsone, digitoxin, theophylline, erythromycin, protease inhibitors
Macrolides, phenytoin, rifampicin (rifampin)	3A4 (induction)	Accelerated cleavage of cyclosporin, erythromycin, antihistamines, azoles, protease inhibitors
Rifampicin	3A (induction)	Increased metabolism of dapsone to a strong oxidant hydroxylamine leading to methaemoglobinaemia

CYP = cytochrome P450.

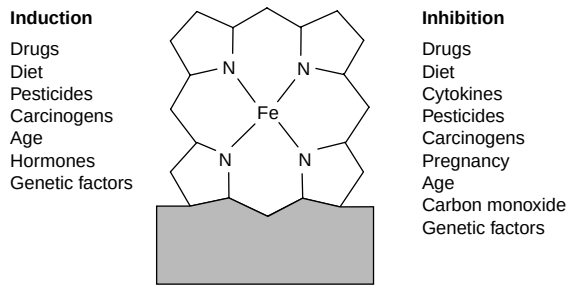

Fig. 1. The prosthetic group of the cytochrome P450 in the endoplasmic reticulum is a porphyrin. Different factors influence its activity.

the activity of this hepatic enzyme reflect its inducibility by a wide range of factors. Even the interaction of a single drug with CYP isoenzymes can be very complex. For example, the H_2 antagonist cimetidine inhibits CYP2D6, CYP3A4, CYP1A2 and CYP2C9.[15] Furthermore, drugs can modulate the activity of several CYP isoenzymes while being metabolised by another, as is the case for quinidine, which inhibits CYP2D6 while being a substrate for CYP3A4. Also, many β-blockers inhibit CYP2D6-dependent activity, but only a few of them are metabolised by this enzyme.[15]

Xenobiotic-metabolising enzymes also exhibit substantial genetic polymorphisms that can explain the variability of their basal activity and their inducibility in a population.[15] Interestingly, polymorphisms of xenobiotic-metabolising enzymes do not become clinically relevant until exposure to the relevant drug. This is the case for CYP2D6 (debrisoquine hydroxylase), where at least 6 different mutations causing lack of enzymatic activity have been described.[16] The consequences of such CYP deficiency also depend on the nature of the drug metabolised. It may cause an exaggerated or even fatal response because of failure of drug elimination (e.g. perhexiline, sparteine), or it may cause a lack of response because of a failure of prodrug activation (e.g. codeine is not converted to morphine).[16]

Conversely, polymorphisms of drug receptors are manifested in the activities of specific xenobiotic-metabolising enzymes even prior to exposure to the relevant drug, as is the case for the arylhydrocarbon (Ah) receptor, which is responsible for the regulation of the activity of several enzymes.[16] The importance of these polymorphisms becomes apparent when considering that these enzymes are responsible for the inactivation and elimination of numerous xenobiotics. Compared with expression polymorphisms of enzymes, alterations of receptor structure are potentially lethal since they interact much more tightly with the intracellular signal transducing system.

The advantages resulting from the polymorphisms of expression of xenobiotic-metabolising enzymes are most impressive in insects, which very rapidly become resistant to toxic pesticides.[16] This polymorphism may also explain why interactions at the level of drug metabolism are much more common than pharmacodynamic interactions.

In dermatology, some of the most important drug-drug interactions mediated by CYP isoenzymes are those involving azole derivatives, cyclosporin, erythromycin and antihistamines, such as terfenadine, astemizole and loratadine. All of these drugs interact strongly with CYP3A4, either by inhibiting its activity (azoles) or by being substrates (cyclosporin, erythromycin and antihistamines). This is of clinical relevance, since the inhibition of CYP3A4 by azoles may lead to increased plasma concentrations of, and adverse effects from, concomitantly administered drugs. The delayed metabolism of loratadine appears to cause no increased toxicity, and it seems to be the most suitable for combination with azoles in cases where such agents have to be administered concomitantly. Ad-

ditionally, loratadine is also metabolised by CYP2D6.

Furthermore, dietary constituents modulate the activity of CYP isoenzymes. The flavonoid naringenin, responsible for the bitterness of grapefruits, is of special relevance here since it inhibits the activity of CYP3A4.[17] On the other hand, rifampicin (rifampin) is a powerful inducer of CYP3A4, and can alter the bioavailability of cyclosporin[8] and azole derivatives.[14,18]

Another very important topic concerning drug interactions in dermatological practice is the treatment of allergic diseases with antihistamines. This group of drugs is well known to exhibit a variety of adverse effects that should be considered before prescription. Drug-drug interactions involving certain antihistamines may have potentially fatal consequences. Certain antihistamines, for example terfenadine, have high membrane permeability and can provoke cardiotoxicity by inhibiting the potassium channel, similar to quinolones or local anaesthetics.[19-21] The risk of experiencing these adverse effects can be amplified by concomitant administration of terfenadine with astemizole, ketoconazole, itraconazole or erythromycin, since they inhibit the CYP3A4-mediated hepatic cleavage of terfenadine leading to its accumulation (fig. 2).[20,21] This drug-drug interaction has led to a search for alternative agents. Indeed, a metabolite of terfenadine, fexofenadine, without the cardiac effects has been introduced.[5,22] This metabolite does not undergo hepatic metabolism and, therefore, is not affected by other drugs interacting with the hepatic CYP system. In the US, the Food and Drug Administration has requested that terfenadine be withdrawn from the market. This example illustrates that recognition of drug-drug interactions and an improved knowledge of the CYP isoenzyme system may lead to better and safer pharmacotherapy.

Azoles have been shown to exhibit a variety of drug interactions important for the prescribing clinician. These occur at the level of metabolism as well as absorption (section 2.1). Ketoconazole is an azole antifungal derivative that binds strongly to human CYP isoenzymes and therefore may cause interactions, whereas the structurally related itraconazole and fluconazole are better tolerated since the latter compounds bind much more avidly to fungal than to human CYP isoenzymes. Therefore, ketoconazole should not be combined with cyclosporin. Even during coadministration of itraconazole and fluconazole, the possible accumulation of cyclosporin has to be monitored. Similar effects have to be considered for concomitant use of cyclosporin with macrolides, rifampicin, phenytoin and carbamazepine.[23,24]

Since the systemically administered antimycotic griseofulvin induces the metabolic activity of var-

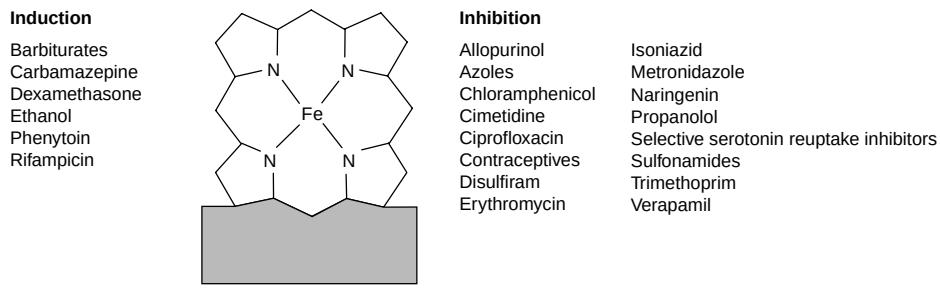

Fig. 2. Drugs, food components and other chemicals can interact with cytochrome P450 (CYP). The major enzyme in the human liver is CYP3A4. It is inducible by, for example, griseofulvin, corticosteroids and rifampicin (rifampin) and can be inhibited by, for example, azoles, ciprofloxacin, erythromycin and naringenin. Important substrates of this enzyme are antihistamines, such as terfenadine, astemizole and loratadine. Loratadine is also metabolized by CYP2D6, which can be inhibited by cimetidine and β-blockers. Theophylline is a substrate for CYP1A2, which can be inhibited by cimetidine and gyrase inhibitors such as ciprofloxacin. Ethanol induces CYP2E1, which also metabolizes paracetamol (acetaminophen).

ious CYP isoenzymes, it can accelerate the metabolism of oral contraceptives,[25] anticoagulants[26] or phenobarbital.[27] Similarly, rifampicin can inhibit the efficacy of oral contraceptives.[25]

Clarithromycin, like erythromycin, is both cleared by and inhibits CYP isoenzymes.[28] This may increase blood concentrations of drugs metabolised through CYP isoenzymes, including theophylline, warfarin, cyclosporin, terfenadine, carbamazepine and benzodiazepines, leading to serious or even life-threatening adverse effects.[28] Azithromycin does not appear to be involved in such interactions, making it a useful alternative to clarithromycin in patients treated with one of these drugs.[29]

Griseofulvin and ketoconazole also interact with CYP2E1, a major ethanol-metabolising enzyme. Accordingly, concomitant intake of these drugs with alcohol can cause disulfiram-like effects.[8,13] Much more complex and potentially hazardous are interactions between alcohol and paracetamol (acetaminophen), which is frequently used in patients who are intolerant to conventional analgesics. Paracetamol is metabolised by CYP2E1 to a highly cytotoxic hydroquinone derivative that can cause hepatocellular necrosis. This toxic compound binds to glutathione.[13,15]

Another example of a drug with a low therapeutic index and possible drug-drug interactions related to its metabolism is theophylline. Since theophylline is metabolised by CYP1A2, interactions can occur with cimetidine, gyrase inhibitors such as ciprofloxacin, enoxacin, and to a lesser extent ofloxacin, as well as compounds in tobacco.[6] Furthermore, in patients with infectious diseases or receiving influenza vaccines, endogenous interferons may inhibit CYP1A2.[3] In all patients receiving theophylline in combination with one of these agents, theophylline serum concentrations should be monitored.

Another drug frequently used in dermatology is the sulfone derivative dapsone. It is metabolised by CYP3A4 to a hydroxylamine derivative. This metabolite is a powerful oxidant and can cause serious adverse effects such as methaemoglobinaemia and agranulocytosis. Combination with rifampicin, which is recommended by the World Health Organization for treatment of lepromatous leprosy, increases the risk of these adverse effects. The combination of dapsone with ketoconazole, cimetidine or grapefruit juice may reduce the risk of dapsone toxicity, since these drugs inhibit CYP3A4.[15]

A recently developed group of drugs pertinent to dermatology practice are the retroviral protease inhibitors saquinavir, ritonavir, nelfinavir and indinavir. These drugs suppress HIV-1 replication through interference with viral protease. Because saquinavir is metabolised by CYP3A4, coadministration of inducers of CYP3A4, such as rifampicin, dexamethasone and benzodiazepines decreases the plasma concentrations of saquinavir. Since corticosteroids are usually not administered systemically to patients with HIV infection, the interaction between these drugs is merely of academic interest. Conversely, rifampicin, a drug commonly used for the treatment of tuberculosis, which occurs in patients with AIDS more frequently than in the general population, must not be coadministered with saquinavir.

In contrast, CYP3A4 inhibitors such as the azoles, erythromycin and sulfonamides may increase plasma concentrations of protease inhibitors to potentially hazardous levels. Also, ritonavir exhibits significant inhibitory effects on CYP3A4 and thus can be administered to increase concentrations of drugs metabolised through this system, including the other protease inhibitors.[30] Therefore, ketoconazole and ritonavir should not be combined with drugs such as terfenadine, astemizole and cisapride, since fatal arrhythmias may occur as a result of inhibited metabolism of these drugs.

Indinavir and nelfinavir appear to be much weaker inhibitors of the CYP3A4 than is ritonavir. Interestingly, the metabolism of indinavir in the intestine is strongly inhibited by ketoconazole, and the finding of an anti-rat CYP3A1 antibody in the intestine and liver induced by dexamethasone suggests the involvement of CYP3A isoforms in both organs.[31]

Non-nucleoside reverse transcriptase inhibitors (NNRTIs) also modulate the activity of CYP3A4

or are metabolised by this enzyme. Therefore, delavirdine should not be coadministered with rifampicin, rifabutin, didanosine and other CYP3A4 inducers. When NNRTIs are combined with saquinavir and indinavir, the serum concentrations of the protease inhibitors can increase because of competition for binding to CYP3A4.[32] The dosage of indinavir may be reduced, but that of saquinavir does not have to be altered. Nevirapine is another NNRTI that is a strong inducer of CYP3A4, and should therefore not be coadministered with drugs that are substrates for this enzyme.[33] In combinations of nevirapine or efavirenz with indinavir, the dosage of the protease inhibitor should be increased; ritonavir concentrations are decreased only by 11%, and increased dosages are not required.[34,35] Finally, it should be emphasised that most of the interactions that could occur with antiretroviral agents have not yet been well studied, and other interactions may be still be unrecognised.

Another very important drug-drug interaction can occur during concomitant administration of azathioprine, commonly used for the therapy of systemic lupus erythematosus and dermatomyositis, and allopurinol. The latter inhibits xanthine oxidase and thereby the cleavage of purines to folic acid. Accordingly, the cleavage of 6-mercaptopurine, a metabolite of azathioprine, is also inhibited, leading to its accumulation and enhancement of its cytotoxic activity. To prevent this, the dosage of azathioprine should be reduced by one-quarter to one-third.[36]

Retinoids are used both topically and systemically in dermatological therapy (see Roos et al.,[6] for review). Concomitant treatment with retinoic acid derivatives (e.g. tretinoin and isotretinoin) and vitamin A (retinol) may lead to hypervitaminosis A. This may be explained by a feedback inhibition of retinol dehydrogenase and a saturation of the binding capacity of the serum retinol-binding protein.[6] Conversely, the efficacy of retinoids in clinical treatment can be increased by concomitant treatment with inhibitors of retinoic acid 4-hydroxylation, such as azole derivatives or vitamin D analogues.[6] This strategy is being used with great clinical success and increasing frequency in the therapy of plaque psoriasis.

Finally, it should be mentioned that the hepatotoxicity of methotrexate is increased by combination with retinoids. Intensive studies to identify the cause of this interaction have been unsuccessful.[37,38] However, retinoids and methotrexate should not be used concomitantly.

2.4 Elimination

Of the interactions of this type (table VII), the combination of methotrexate and nonsteroidal anti-inflammatory drugs (NSAIDs) is of great importance in dermatology. Inhibition of prostaglandin synthesis by NSAIDs may disturb the renal tubular

Table VII. Drug interactions during elimination

Drug	Interacting drug	Effects
Amphotericin	Pentamidine (and other nephrotoxic drugs)	Disturbed renal function
Azoles	Corticosteroids	Increased plasma corticosteroids
Fluconazole	Thiazides	Increased plasma fluconazole
Methotrexate	Cyclosporin	Nephrotoxicity (possibly pharmacodynamic)
Methotrexate	NSAIDs, probenecid, salicylates	Inhibition of prostaglandin synthesis, increased plasma methotrexate
Methotrexate	Penicillin	Decreased methotrexate clearance leading to increased plasma concentrations
Probenecid	Aciclovir, cidofovir, ganciclovir, foscarnet	Inhibition of renal elimination and increased plasma concentration of antiviral drugs
Quinolones	Procainamide	Increased plasma procainamide
Tetracyclines	Urinary alkalinisers	Decreased plasma tetracycline concentrations

NSAIDs = nonsteroidal anti-inflammatory drugs.

elimination of methotrexate, leading to plasma accumulation of this drug with destruction of renal parenchyma.[7] This type of adverse effect should be kept in mind, especially since combination of these drugs might appear to be one option for therapy of psoriatic arthritis. Concomitant use of these drugs must be avoided. Although the nephrotoxicity of methotrexate in combination with cyclosporin can be related to their pharmacodynamic effects, the exact mechanism of this interaction is not known.

Since the use of intravenous amphotericin is related to a high incidence of abnormal renal function, it should not be used with other nephrotoxic drugs. Acute, rapid progressive renal failure has been documented after simultaneous use of intravenous amphotericin and intravenous pentamidine in HIV-infected patients.[39]

Another type of adverse effect during antiviral therapy involves aciclovir, ganciclovir, foscarnet and cidofovir in combination with drugs inhibiting renal tubular secretion, such as probenecid. This combination reduces the renal clearance of the antiviral agents, leading to an increase in their plasma concentrations and thereby to an increased risk of drug toxicity. Similarly, thiazide diuretics inhibit the renal elimination of fluconazole, leading to potentially hazardous elevated plasma concentrations of the latter drug and adverse effects such as headaches, nausea, vomiting, and alterations of hepatic and renal function parameters.[40]

Conversely, urinary alkalinisers can decrease plasma concentrations of tetracyclines by increasing their renal elimination.

3. Conclusions and Future Perspectives

The most important drug interactions with regard to the therapy of dermatological diseases are shown in table VIII.

Awareness of drug-drug interactions is the first step in reducing or eliminating the risk of their occurrence. One possible approach to reducing the risk of drug-drug interactions that relate to drug metabolism would be to fully characterise genetic and environmental effects on CYP isoenzyme expression in human populations. The use of molecular biological approaches may provide us in the near future with tools to determine the individual activities of xenobiotic-metabolising enzymes in individual patients, facilitating the development of drugs for certain patients groups.[15] Such a 'molecular read-out' could help to identify subpopulations at increased risk of such interactions.

Table VIII. Most important drug interactions in the therapy of dermatological diseases

Antiviral drugs (e.g. aciclovir, cidofovir, ganciclovir and foscarnet) and inhibitors of renal tubular secretion (e.g. probenecid)
Azathioprine with inhibitors of xanthine oxidase
Griseofulvin with azoles
Methotrexate with trimethoprim, probenecid, cyclosporin, NSAIDs and retinoids
Non-nucleoside reverse transcriptase inhibitors with other drugs metabolised by CYP3A4 (e.g. nevirapine, efavirenz or delavirdine with indinavir)
Protease inhibitors with azoles, sulfonamides and other modulators of CYP3A4 activity
Rifampicin (rifampin) with sulfones (e.g. dapsone)
Terfenadine, astemizole, loratadine and older antihistamines with drugs that modulate CYP3A4 activity (azoles, erythromycin, cyclosporin and grapefruit juice)
Tetracyclines and retinoids

CYP = cytochrome P450; **NSAIDs** = nonsteroidal anti-inflammatory drugs.

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