Pharmacokinetics

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Pharmacokinetics analyzes the path of drugs through the organism and the effects of the organism on drugs. The pharmacokinetic properties of a drug are described by the ADME parameters. To ensure good intestinal absorption and BBB penetration, a drug must be of low molecular mass, neutral, and lipophilic. The first-pass effect describes inactivation of a drug during the first liver passage. CYP inhibition enhances the effects of drugs that are inactivated via the same CYP, whereas CYP induction reduces drug effects. A large distribution volume points to a deep compartment in which a drug accumulates. Prodrugs are inactive precursors of a drug which are metabolically converted to the active drug. The enterohepatic circulation is a cyclic process of biliary elimination and consequent intestinal reabsorption of a drug. In general, a drug for oral administration should possess good bioavailability, a moderately sized distribution volume, and a plasma half-life that allows for good controllability, but no enterohepatic circulation. For treatment of CNS diseases, drugs must penetrate the BBB, whereas for treatment of non-CNS diseases, a lack of BBB penetration is desirable.

Key Points

1. Most drugs are absorbed and eliminated according to first-order kinetics following oral administration.
2. The first-pass effect can be exploited for pharmacotherapy.
3. The properties of the BBB can be exploited to reduce ADRs in the CNS.
4. With a first-order kinetics, steady-state concentration of a drug is achieved after 4–5 plasma half-lives.
5. High plasma protein binding of a drug, via competition with other drugs, can lead to ADRs.
6. TDM increases drug safety.
7. The best way to minimize drug interactions is to avoid polypharmacy.
8. CYP polymorphisms can increase or reduce drug effects.
9. Liver failure and CKD can prolong drug effects and cause ADRs.
10. MRPs contribute to resistance against classic cytostatics.
11. In meningitis, babies and toddlers, xylometazoline, MCP, and loperamide are risky due to ADRs in the CNS.
12. Amiodarone is a problematic drug with an extremely long plasma half-life, substantial risk of accumulation, and many ADRs.
13. RMP, carbamazepine, phenytoin, phenobarbital, St. John's wort, and nicotine are classic CYP inducers.
14. Ciprofloxacin, azole antimycotics, erythromycin, clarithromycin, and grapefruit juice (naringin) are classic CYP inhibitors.
15. Therapy with drugs possessing a small therapeutic index such as mGPCR antagonists, theophylline, ciclosporin, and phenprocoumon are prone to CYP interactions.

2.1 ADME Parameters: Pharmacotherapeutic Relevance

Pharmacokinetics describes the path of drugs through the organism and the effects of the organism on the drug. Pharmacokinetics comprises the parameter absorption, distribution, metabolism, and elimination. These parameters influence the pharmacological effects of a drug in the organism. Pharmacokinetic processes follow zero-order or first-order kinetics. In a zero-order kinetics, a constant amount of drug is absorbed or eliminated per time interval. The classic example of a zero-order absorption is the i.v. infusion of a drug. The classic example of a zero-order elimination is the degradation of ethanol by ethanol dehydrogenase. In a first-order kinetics, drugs are absorbed or eliminated concentration-dependently; the kinetics follows an exponential function.

The plasma half-life is the time interval in which the concentration of a drug is reduced by 50%. Accordingly, after two half-lives, the concentration is reduced to 25%, after three half-lives to 12.5%, and after four half-lives to 6.25%. In an open system like the human organism, with first-order absorption and elimination kinetics, after 4–5 plasma half-lives, an equilibrium

between absorption and elimination is reached, resulting in a steady-state drug concentration.

Figure 2.1 provides an overview of the ADME parameters. In most cases, a drug is administered orally. The most important organ for absorption is the small intestine. To avoid inactivation of drugs by low pH in the stomach, many drugs are applied as acid-resistant formulations. Drug therapy should be as convenient as possible for the patient. Whenever possible, drugs should be given once daily. For many chronic diseases such as hypertension (see ▶ Chap. 15), CHF (see ▶ Chap. 16), and hypo- and hyperthyroidism (see ▶ Chap. 21), it is important to achieve a constant drug effect. Therefore, many drugs are applied as extended-release formulations. Most drugs are absorbed by diffusion. Prerequisites for absorption by diffusion are low molecular mass (<300 Dalton), sufficient lipophilicity, and neutral form of the drug. In several cases, drug absorption can be improved by application of a lipophilic prodrug. Following absorption in the intestine, the prodrug is cleaved in the organism and the active drug is liberated. Many prototypical prodrugs are esters that are hydrolyzed by esterases.

GI absorption is influenced by many factors. An accelerated intestinal passage (co-application of laxatives or prokinetics, antibiotic-associated diarrhea, inflammatory bowel diseases; see ▶ Chap. 13) can reduce drug absorption. This can lead, e.g., to the loss of effectiveness of oral contraceptives (see ▶ Chap. 24). Fat food may delay drug absorption. For some drugs (thyroid hormones, ▶ Chap. 21; bisphosphonates, ▶ Chap. 20; PPI, ▶ Chap. 13) it is essential to apply them on an empty stomach in order to ensure good intestinal absorption. Certain drugs, most notably tetracyclines (see ▶ Chap. 33) and bisphosphonates (see ▶ Chap. 20), interfere with calcium absorption and must not be taken together with calcium or milk. GCR agonists for the therapy of autoimmune diseases are given in the morning to suppress the hypophysis function as little as possible (see ▶ Chap. 11).

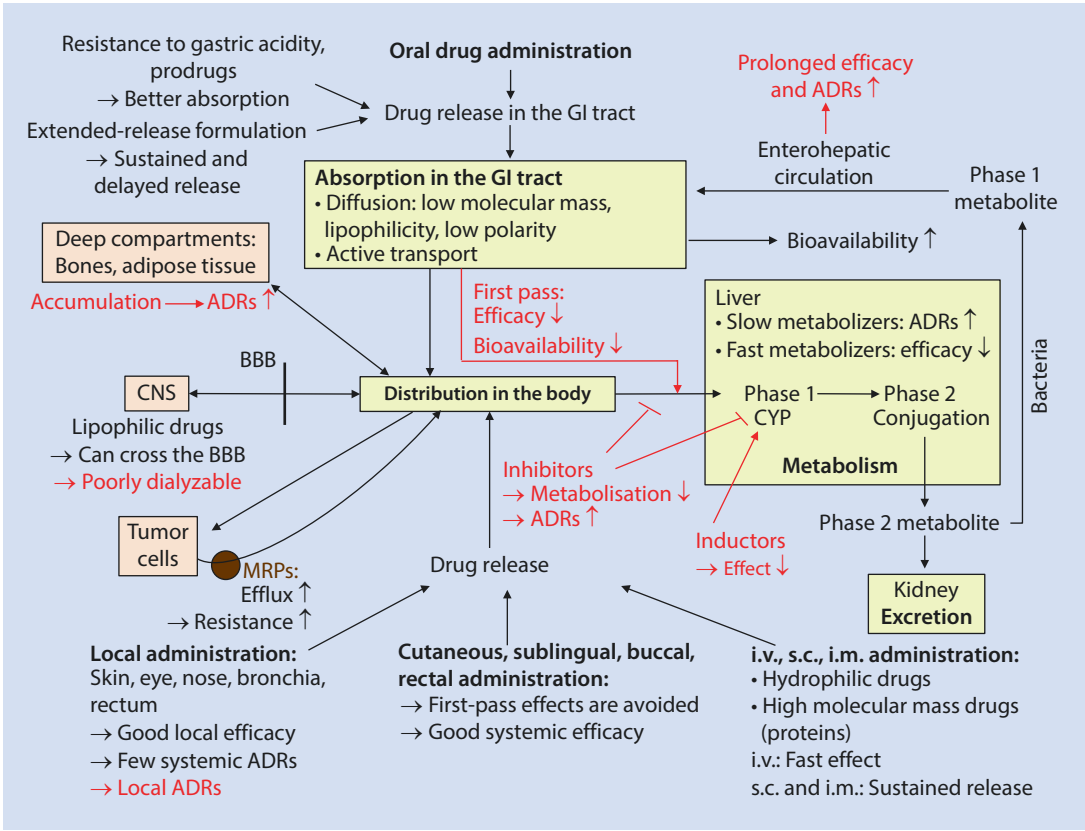

Fig. 2.1 Overview of pharmacokinetics of drugs in the organism: Pharmacotherapeutic relevance of the ADME parameters. Many ADRs are due to unfavorable ADME parameters

High-molecular mass drugs (most notably proteins such as insulin and therapeutic antibodies; see ▶ Chaps. 11, 19, and 32) and very hydrophilic drugs like ions have to be administered parenterally (mostly s.c.). Common ADRs of s.c. injection are local allergic reactions and tissue induration (see ▶ Chaps. 3, 11, 19, and 32). I.m. injections are used for application of certain sex hormones (see ▶ Chap. 24) and mGPCR antagonists (see ▶ Chap. 29). For therapy of eye diseases (see ▶ Chap. 31), respiratory tract diseases (see ▶ Chaps. 5, 7, and 14), vaginal diseases (see ▶ Chaps. 24 and 35), skin diseases (see ▶ Chap. 11), and rectum diseases (see ▶ Chap. 13), local drug administration is feasible in many cases. Advantages are that high local drug concentrations can be achieved and that in general, ADRs are just of local nature.

Following absorption in the small intestine, the drug reaches the liver. Metabolism of the drug begins already during the first liver passage. Inactivation of a drug during the first liver passage is referred to as the first-pass effect. Because of its high clinical relevance, the first-pass effect is dealt with in a separate section (see ▶ Sect. 2.2). The percentage of an orally applied drug that reaches the systemic circulation after the first liver passage is referred to as bioavailability. In general, bioavailability of a drug should be high. Following i.v. injection bioavailability amounts to 100%. The onset of drug action after i.v. injection is fast and reliable. This is routinely exploited in anesthesia and emergency medicine (see ▶ Chaps. 3, 5, 10, 16, 17, 19, and 27). However, i.v. application of drugs can also result in problems such as TdP (see ▶ Chap. 17) and should therefore be performed slowly.

After the first liver passage, the drug is distributed in the organism and reaches its target organs, unless the liver is the primary target (see ▶ Chaps. 22 and 34). Distribution depends on the physiochemical properties of the drug (charge, lipophilicity, molecular mass), pH, binding to plasma proteins, organ perfusion, membrane permeability, age, and nutritional status. Local anesthetics are an example of pH-dependent drug distribution (see ▶ Chap. 26). White adipose tissue constitutes a large compartment in which lipophilic drugs accumulate. As a consequence, in many obese patients, drug doses must be increased.

The distribution volume is a virtual volume, describing the apparent volume in which the drug is distributed. A distribution volume of 4 l implies that the drug is distributed in the intravasal space; a distribution volume of 12.5 l implies that the drug is distributed in the extracellular space. A distribution volume of 70–80 l indicates that the drug is distributed in the entire organism and a distribution volume > 80 l points to deep compartments. For pharmacotherapy, deep compartments are problematic because they point to retention of a drug in the organism (e.g., in adipose tissue or bone) and can be the cause of long-term ADRs. A drug is mobilized only slowly from deep compartments. A classic example is the class I–IV antiarrhythmic drug amiodarone (see ▶ Sect. 2.4 and ▶ Chap. 17). Tetracyclines form complexes with calcium and, when applied to a pregnant woman, can accumulate in the bones and teeth of the fetus (see ▶ Chap. 33). Another example of a drug accumulating in a deep compartment is thiopental (see ▶ Chap. 27). After i.v. injection, thiopental rapidly reaches the CNS, followed by redistribution into the skeletal muscles and later the adipose tissue. From the latter compartment, thiopental is released slowly. Thus, following a single long-term application or repeated administration, thiopental can cause prolonged sedation. In case of bisphosphonates (see ▶ Chap. 20), the deep compartment (accumulation in osteoclasts) contributes to the long-term protective effects in osteoporosis.

Binding of a drug to plasma proteins reduces the percentage of the free drug that is pharmacologically active. If two drugs with high plasma protein binding compete against each other, a small therapeutic index of one of the drugs becomes problematic. As a result, the free concentration of this drug increases, and serious ADRs can occur. A classic example is competition of the VKA phenprocoumon (see ▶ Chap. 18, plasma protein binding >99%) that competes with other strongly protein-bound drugs such as ASA (see ▶ Chap. 18) or the oral antidiabetic glibenclamide (see ▶ Chap. 19). Via displacement from plasma proteins, phenprocoumon becomes more effective at inhibiting the synthesis of active coagulation factors, ultimately increasing the risk of serious hemorrhage. This risk is further increased by ASA because this drug inhibits platelet aggregation (see ▶ Chap. 18). Therefore, for pharmacodynamic and pharmacokinetic reasons, the combination of a VKA and ASA is contraindicated. If glibenclamide is displaced from plasma proteins

by phenprocoumon, serious hypoglycemia can result. Thus, the combination of drugs with high plasma protein binding should be avoided.

The goal of tumor therapy is to selectively destroy tumor cells without harming normal cells (see ▶ Chap. 32). Via exploitation of specific receptors, enzymes, and biochemical mechanisms, it is now possible to discriminate between tumor cells and normal cells at least to a certain degree. However, tumor cells possess efficient mechanisms to evade the deleterious effects of tumor therapeutics. MRPs expressed at the plasma membranes are of great relevance for tumor resistance. MRPs export many classic cytostatic drugs from tumor cells and, thereby, reduce drug efficiency. Unfortunately, it is not yet possible to selectively inhibit MRP in tumor cells to avoid export of classic cytostatics. To circumvent the problem, various drugs are combined, delaying the selection of tumor cells with high MRP activity.

The liver is the main organ for drug metabolism. Drug metabolism is divided into two phases. In phase 1, the drug is oxidized, reduced, or hydrolyzed. Phase 1 metabolites can be pharmacologically active or inactive. In phase 2, the phase 1 metabolite is conjugated with glucuronic acid, acetic acid, sulfuric acid, or an amino acid. Via conjugation, the phase 1 metabolite (with few exceptions; morphine-6-glucuronide; see ▶ Chap. 10) becomes inactive and water-soluble. The phase 2 metabolite is then excreted via the kidney and/or bile.

In liver diseases such as hepatitis C (see ▶ Chap. 34), liver cirrhosis, and intoxication with hepatotoxic drugs such as paracetamol (see ▶ Chaps. 4 and 10) and in newborns, the metabolic capacity of the liver is reduced. Accordingly, the duration of action of drugs is increased and the drug dose must be reduced.

CYPs play a major role in phase 1 metabolism. CYPs are hemoproteins with monooxygenase activity. CYPs also play an important role in steroid hormone metabolism (see ▶ Chaps. 24 and 35). The human genome possesses more than 50 CYP genes. CYPs are classified with a *number-letter-number* code. The first number designates the gene family, the letter describes the gene subfamily, and the last number designates the individual gene.

CYP expression is regulated by NRs such as the pregnane X receptor (PXR) (see ▶ Chap. 1) which binds many xenobiotics including drugs, stimulates CYP expression, and, as a result, promotes drug inactivation. CYP activity shows substantial interindividual variations.

There are CYP polymorphisms with very high enzymatic activity (ultrafast metabolizers) and polymorphisms with very low activity (poor metabolizers). CYP polymorphisms play a major role in the responsiveness of individual patients to drugs. For example, in an ultrafast metabolizer for CYP2D6, tamoxifen is inactivated very rapidly and hence ineffective (see ▶ Chaps. 24 and 32). Conversely, in a poor metabolizer for CYP2C9, VKAs and COX inhibitors are inactivated more slowly, resulting in more serious ADRs (see ▶ Chaps. 10 and 18). Therefore, in case of unexpected lack of drug efficacy or serious ADRs, TDM is indicated. CYP interactions are clinically so important that there are being dealt with in a separate section (see ▶ Sect. 2.5).

The bile is an important elimination pathway for drugs. Biliary eliminated phase 2 metabolites reach the intestine where bacteria can deconjugate the drugs to more lipophilic phase 1 metabolites. These metabolites can be reabsorbed and become pharmacologically active. In this way, an enterohepatic circulation is established, prolonging drug action. In general, enterohepatic circulation is undesirable because it increases the risk of ADRs, specifically in cases of overdosing. Enterohepatic circulation can be interrupted by absorbents (see ▶ Chaps. 4 and 22). Digitoxin (see ▶ Chap. 16), tamoxifen (see ▶ Chaps. 24 and 32), carbamazepine (▶ Chap. 28), leflunomide (see ▶ Chap. 11), and NSMRIs (see ▶ Chap. 28) are drugs with large enterohepatic circulation.

The kidney is the major organ for drug elimination (phase 2 metabolites). Elimination is accomplished via glomerular and tubular secretion. In CKD, drug elimination is delayed, and accordingly, drugs can accumulate and serious ADRs can occur. This requires individually adapted dose reduction. CKD is so important for drug therapy that it is discussed in a separate chapter (▶ Chap. 12).

2.2 Significance of the First-Pass Effect

Table 2.1 summarizes the properties of some drugs with high first-pass effect. For p.o. administration, a high first-pass effect is disadvantageous because the drug cannot act sys-

Table 2.1 Significance of the first-pass effect for drug effects: examples

Drug	Route of administration	Pharmacological properties and pharmacotherapeutic consequences	Further contexts in Chaps.
Budesonide	Inhalation, rectal	Local anti-inflammatory and immunosuppressive effect in asthma and/or UC. After systemic absorption the drug is rapidly metabolized in the liver; therefore systemic ADRs are rare.	11, 13, 14
Estradiol	Transdermal (patch, gel)	Estradiol is the most important physiological ER agonist and is effective in treating peri- and postmenopausal symptoms. Administered orally, estradiol is inactivated to a large extent when it passes through the liver. Applied dermally, estradiol can systemically exert its effects.	24
GTN	Buccal, sublingual, rectal, i.v.	Via these routes, rapid inactivation of GTN in the liver is circumvented, and a short-term relaxing effect on smooth muscle cells is achieved, which can be used in emergency situations.	9
Scopolamine	Transdermal (patch)	Prolonged drug administration through the skin resulting in a prolonged antiemetic effect (e.g., during boat cruises).	5, 7
Simvastatin	p.o.	Simvastatin inhibits HMG-CoA reductase in the liver and thus synthesis of cholesterol. As simvastatin is rapidly metabolized in the liver, systemic ADRs can be minimized (low risk of rhabdomyolysis, provided no CYP3A4 or OATPB1 inhibitors are administered at the same time).	22

The first-pass effect is not always "a problem," but can be exploited for effective pharmacotherapy

temically. However, there is one important exception: HMG-CoA reductase inhibitors that are effective in the therapy of dyslipidemia (see ▶ Chap. 22) primarily exert their effects in the liver. HMG-CoA reductase inhibitors with high bioavailability possess a high risk for rhabdomyolysis. The risk of systemic ADRs of HMG-CoA reductase inhibitors is increased by simultaneous administration of CYP3A4 inhibitors or OATB1 inhibitors that reduce hepatic drug uptake.

GTN is a classic example of a drug with high first-pass effect. GTN does not act systemically upon oral administration. However, the smooth muscle-relaxing effect of GTN can be used in various emergency situations such as AP, hypertensive emergency, and colic pain (see ▶ Chaps. 9, 10, 15, 16, and 23). Several preparations of the drug such as sublingual sprays are available to circumvent the first-pass effect. Compared to sublingual application, the onset of action is delayed upon rectal administration to avoid the first-pass effect. The specific formulation has to be commensurate to the specific indication. Although the liver is circumvented upon buccal, sublingual, dermal, rectal or i.v. application, nonetheless, the liver will be reached soon and drug inactivation commences. As a result, the duration of action of GTN is very limited, i.e., about 30 minutes, but this time interval is sufficient to initiate further therapeutic measures.

Scopolamine is an M_xR antagonist and causes an antimuscarinic syndrome at high doses (see ▶ Chaps. 4 and 5). However, at low doses, scopolamine possesses a good antiemetic effect in kinetosis (see ▶ Chap. 6). Due to its high first-pass effect, this effect cannot be exploited therapeutically when scopolamine is administered p.o. Instead, scopolamine is applied as patch behind the ear. From this depot, scopolamine is released over a long period of time to exert its therapeutic effects while at the same time at least partially circumventing the liver.

Glucocorticoids (GCR agonists) are effective anti-inflammatory and immunosuppressive drugs that are used in autoimmune diseases and asthma and for prevention of organ rejection following

transplantation (see ▶ Chaps. 11, 13, and 14). A major problem in the clinical use of GCR agonists is that these drugs exhibit global effects on metabolism and electrolytes, resulting in serious ADRs (see ▶ Chap. 11). It is the goal of a GCR agonist therapy to focus the drug effects on the diseased organ. This goal can be accomplished on the one hand via local administration (see ▶ Chaps. 13 and 14) and on the other hand by application of GCR agonists that are rapidly inactivated in the liver following systemic absorption.

Additionally, sex hormones (estrogens, gestagens, and androgens) are rapidly inactivated in the liver following oral administration. One option to compensate for the first-pass effect is to administer high drug doses (e.g., gestagens). Another strategy is to apply the drugs locally via patches, thereby circumventing the first-pass metabolism at least partially (see ▶ Chap. 24).

2.3 Significance of the Blood-Brain Barrier (BBB)

The BBB constitutes a physiological barrier between the systemic circulation and the CNS. Tight junctions between endothelial cells prevent paracellular diffusion of drugs. Accordingly, drugs have to penetrate both endothelial membranes. Endothelial cells are located above the basal membrane. On the contralateral side of the basal membrane are glia cells that provide an optimal milieu for neurons and protect them from toxic compounds. Drugs can penetrate the BBB via diffusion and via transport processes.

Table 2.2 shows how differential BBB penetration impacts on the therapeutic use of various drugs. For treatment of CNS diseases (see ▶ Chaps. 25, 28, 29, and 30) and for anesthesia (see ▶ Chap. 27), it is essential that drugs penetrate the BBB. Most drugs reach the CNS via diffusion. Prerequisites for diffusion are low molecular mass (< 300 Dalton), sufficient, but not too high lipophilicity, and neutral drug species. A disadvantage of high lipophilicity of CNS-active drugs is that in case of intoxication, they cannot be rapidly eliminated, e.g., via dialysis (see ▶ Chap. 4). The presence of too many polar groups and a high molecular mass impede with the penetration of the BBB. In meningitis, permeability of the BBB is increased. This facilitates therapy with antibiotics that normally do not penetrate well into the CNS, most notably β-lactam antibiotics (see ▶ Chap. 33).

In some cases, transport of hydrophilic drugs across the BBB is clinically relevant. Levodopa is transported across the BBB via an amino acid carrier and converted into DA in the CNS. This mechanism is exploited in the therapy of PD (see ▶ Chap. 8). In contrast to levodopa, the DOPA decarboxylase inhibitor carbidopa is not transported into the CNS. Thus, peripheral ADRs caused by levodopa can be reduced by simultaneous application of carbidopa.

In the area postrema, the BBB is leaky so that in this region even hydrophilic drugs can reach the CNS. This is of (patho)physiological significance because activation of various receptors in the CTZ of the area postrema induces vomiting. Accordingly, antagonism of these receptors with hydrophilic drugs that otherwise penetrate the BBB only poorly results in antiemetic effects. The D_2R antagonists domperidone and MCP, the NK_1R antagonist aprepitant, and the $5\text{-}HT_3R$ antagonist ondansetron belong into this group of drugs (see ▶ Chap. 6).

In babies and toddlers, the BBB is not yet fully established physiologically. This implies that drugs that do not penetrate the BBB in school children, adolescents, and adults can reach the CNS very well in babies and toddlers and cause serious ADRs. Babies and toddlers quite often suffer from viral infections of the upper airways. For symptomatic therapy, decongestant nose drops containing α_1AR agonists (prototype xylometazoline) are applied (see ▶ Chap. 5). However, these drugs can penetrate into the CNS and cause hypertension. To avoid this ADR, it is crucial that in babies and toddlers, only nose drops with an approved low drug concentration are applied. In addition, these age groups often suffer from GI tract infections (see ▶ Chap. 13). Whereas in adolescents and adults, short-term symptomatic treatment with antiemetics and prokinetics such as MCP and the peripherally acting MOR agonist loperamide can be performed, these drugs are contraindicated in babies and toddlers. Like antipsychotically acting mGPCR antagonists (see ▶ Chap. 29), these drugs can cause EPSs (acute dyskinesias). Dyskinesias are reversible but are worrisome for the parents. Loperamide, otherwise activating only MOR outside the CNS, can

Table 2.2 Significance of the BBB for drug effects: examples

Drug	BBB penetration	Pharmacological properties and pharmacotherapeutic consequences	Further contexts in Chaps.
AChEIs			
Donepezil	Very good	Donepezil is uncharged and therefore easily penetrates the BBB. In the CNS, donepezil reversibly inhibits AChE and is symptomatically used in the treatment of AD.	30
Neostigmine	Very poor	Neostigmine is a quaternary amine and predominantly positively charged at physiological pH. Thus, it hardly penetrates the BBB and can be used without ADRs in the CNS in the treatment of myasthenia gravis.	5
M_xR antagonists			
Atropine	Moderate	Atropine is a tertiary amine. At high doses in the CNS, atropine can cause confusion, hallucinations, unconsciousness, and respiratory paralysis. Therefore, atropine has to be administered with care in anesthesia. Atropine intoxication in children is observed when they confuse the fruits of the deadly nightshade with similarly looking cherries. For treatment of a CNS atropine intoxication, the AChEI physostigmine, which also penetrates the BBB, can be applied.	4, 5, 17
Butylscopolamine	Very poor	Butylscopolamine is a quaternary amine and predominantly positively charged at physiological pH. Therefore, it hardly penetrates the BBB and can be used without ADRs in the CNS in the treatment of smooth muscle spasms.	5, 13
Scopolamine	Very good	Scopolamine is a tertiary amine. It is predominantly used to prevent motion sickness.	5, 7
Tiotropium	Very poor	Tiotropium is a quaternary amine and predominantly positively charged at physiological pH. Therefore, it hardly penetrates the BBB and can be used without ADRs in COPD therapy.	5, 14
Dopaminergic drugs			
Carbidopa	None	In contrast to levodopa, carbidopa is no substrate for the amino acid transporter and, therefore, cannot enter the CNS. This is why carbidopa effectively inhibits the transformation of levodopa into DA in peripheral organs, thereby reducing peripheral ADRs.	8
Levodopa	Very good	Levodopa passes through the BBB by means of an amino acid transporter and is converted in the CNS to DA. Levodopa is used in the treatment of PD.	8

Table 2.2 (continued)

Drug	BBB penetration	Pharmacological properties and pharmacotherapeutic consequences	Further contexts in Chaps.
MOR ligands			
Heroin (morphine prodrug, MOR agonist)	Excellent	Heroin is highly lipophilic due to the acetylation of two hydroxyl groups of morphine. It, therefore, ultrarapidly and effectively penetrates the BBB, which results in an excellent analgesic effect when administered intravenously. Having reached the CNS, heroin is rapidly mono- or dideacetylated. In some countries (e.g., UK), heroin is approved for pain management. Because of the rapid onset of effects, there is a high risk of heroin addiction.	10
Methylnaltrexone (MOR antagonist)	Very poor	Methylnaltrexone is a quaternary amine and predominantly positive at physiological pH. Therefore, it hardly crosses the BBB. Methylnaltrexone is used to relieve MOR agonist-induced constipation without attenuating the central analgesic effect.	10, 13
Morphine (MOR agonist)	Poor - moderate	Because of moderate lipophilicity and rapid glucuronidation, the CNS penetration of morphine is only poor to moderate. Particularly p.o. administration is associated with a slow onset of the analgesic effect, which is no problem in long-term pain management. However, in cases of acute pain, morphine has to be administered i.v. As morphine only slowly penetrates the BBB, the risk of addiction is only low, particularly when morphine is administered p.o. in pain management.	10
Naltrexone (MOR antagonist)	Excellent	Naltrexone is a tertiary amine and predominantly positively charged at physiological pH. It is relatively lipophilic and easily penetrates the BBB. Naltrexone antagonizes the agonist effects at the MOR. Because of its long duration of action, naltrexone is predominantly used in relapse prevention after morphine/heroin withdrawal treatment.	10

The BBB can be exploited for effective pharmacotherapy and minimization of ADRs

cause respiratory depression in babies and toddlers (see ▶ Chap. 13).

Atropine is an example of a drug with moderate BBB penetration. Atropine is primarily used in anesthesia and cardiology for treatment of bradycardia (see ▶ Chaps. 5 and 17). There is no therapeutic application of atropine for CNS diseases; for the CNS, atropine is just a poison. Introduction of an isopropyl group into atropine yields isopropylatropine (ipratropium). Due to the quaternary amino group, the latter drug does not penetrate into the CNS and can be applied via inhalation for the treatment of asthma and COPD without the risk of ADRs in the CNS. With further chemical modifications, keeping the quaternary amine function, ipratropium was developed into tiotropium that possesses a particularly long duration of action (see ▶ Chap. 14).

The BBB is also exploited with another M_xR antagonist. Scopolamine is a tertiary amine that penetrates the BBB well and is used for the treatment of kinetosis (see ▶ Chap. 6). Via butyrylation scopolamine is converted into butylscopolamine. This drug does not penetrate the BBB but can be effectively used to treat colic pain caused by the contraction of smooth muscle cells (GI tract, gall bladder, and ureteric colic and menstrual pain) (see ▶ Chaps. 5, 13, and 23). The positive charge

also reduces absorption following p.o. administration. Therefore, for severe colic pain, butylscopolamine is administered i.v.

One feature of AD is degeneration of cholinergic neurons (see ▶ Chap. 30). Accordingly, one therapeutic strategy aims at improving the function of the remaining cholinergic neurons. This can be accomplished by the AChEI donepezil that penetrates the BBB. In contrast to AD, in myasthenia gravis it is important to inhibit AChE exclusively in the periphery to enhance the function of the remaining nAChR and the neuromuscular end plate (see ▶ Chap. 5). This goal can be accomplished by administration of AChEIs that possess a quaternary nitrogen (prototype neostigmine) and, therefore, cannot penetrate the BBB. A disadvantage of the latter drug class is that GI absorption is suboptimal so that GI colic pain can result.

Drugs that exert their effects via MOR (see ▶ Chap. 10) also differ from each other with respect to BBB penetration. The MOR agonist morphine penetrates the BBB only moderately because of its two hydrophilic hydroxyl groups. As result, particularly after p.o. administration, morphine exhibits only a relatively slow onset of analgesic effect. In long-term pain therapy, these properties are actually desired because the risk of addiction and tolerance is particularly high upon rapid accumulation of the drug in the CNS following i.v. injection. Acetylation of the two hydroxyl groups of morphine gives rise to the lipophilic prodrug diamorphine or, briefly, heroin. Following i.v. injection, heroin rapidly accumulates in the CNS and is also rapidly converted in its two active metabolites, monoacetyl morphine and morphine. Following i.v. injection, heroin induces effective analgesia and a short-lasting dreamlike state with euphoria. Therefore, heroin possesses a much higher risk of addiction and tolerance than morphine. For these reasons, in many countries, heroin is not approved for pain therapy. However, in certain countries, e.g., the UK, heroin can be prescribed for severe pain. This is an example of culture-dependent differences in pharmacotherapy in different countries.

To prevent relapse of morphine/heroin addiction following detoxification, the BBB-penetrating MOR antagonist naltrexone is used. Methylation of the tertiary amine results in the formation of methylnaltrexone. This drug does not penetrate the BBB but acts only peripherally. This effect of methylnaltrexone is used in the therapy of morphine-induced constipation which is mediated via intestinal MOR (see ▶ Chaps. 10 and 13).

2.4 Significance of the Plasma Half-Life

After five plasma half-lives, a drug is virtually eliminated from the organism. The plasma half-life is of great importance for pharmacotherapy because it determines the duration of action of many drugs. ◘ Table 2.3 provides examples of drugs with widely different plasma half-lives and implications for pharmacotherapy.

The plasma half-life can range very widely, e.g., from 1 to 2 minutes for remifentanil to 2.5 months for amiodarone. The importance of the plasma half-life depends on the specific indication. For example, because of its extremely short half-life, the MOR agonist remifentanil is excellently suited for intraoperative analgesia with a very short postoperative recovery period (see ▶ Chaps. 10 and 27). The drug is applied as i.v. infusion, and the dose can be rapidly adjusted according to individual requirements. For long-term therapy of chronic pain, p.o. administered morphine in extended-release formulation having a duration of action of 8–10 hours is suitable (see ▶ Chap. 10).

For symptom-oriented therapy of pain, the COX inhibitor ibuprofen with its short plasma half-life of 2 hours is well suited (see ▶ Chap. 10). Because of this property, ibuprofen is widely used in the treatment of acute pain such as toothache, postsurgical pain, and pain after injuries to flexibly adapt the drug dose to the extent of pain. Another advantage of the short plasma half-life of ibuprofen is that ADRs, specifically in the GI tract and kidneys and on blood pressure, are transient. For long-term treatment of chronic pain such as in rheumatic diseases, ibuprofen is not feasible because of its pharmacokinetic properties.

For the treatment of chronic diseases, it is important to ensure a constant drug effect. A good example for this concept is the long-term therapy of hypertension with dihydropyridine-type CCBs (see ▶ Chap. 15). The first CCB of this class, nifedipine, exhibits a good relaxing effect on vascular smooth muscle cells, but its effect is only transient due to the short plasma half-life. Fluctuations in BP and reflex tachycardia result, ultimately lead-

Table 2.3 Significance of the plasma half-life for drug effects: examples

Drug	Plasma half-life	Route of application	Pharmacological properties and pharmacotherapeutic consequences	Further contexts in Chaps.
Analgesics				
Ibuprofen (non-MOR agonist)	2 hours	p.o., rectal, i.v.	Because of its short plasma half-life, analgesic therapy is well controllable, particularly in acute pain management.	10
Remifentanil (MOR agonist)	1–2 minutes	i.v., infusion	Because of its ultrashort plasma half-life, TIVA is very well controllable. Rapid postoperative recovery.	10, 27
CCBs				
Amlodipine	35–50 hours	i.v.	Long-acting dihydropyridine. Because of its long plasma half-life, the drug can be taken once daily and – contrary to nifedipine with its short plasma half-life – a constant BP reduction can be achieved. Because of their constant long-term effects, long-acting dihydropyridines are often used in hypertension treatment.	15
Nifedipine	1–2 hours	buccal, p.o., i.v.	Short-acting dihydropyridine. Because of its short plasma half-life, nifedipine is well suited for the treatment of hypertensive emergency. Long-term hypertension therapy should be avoided because BP fluctuations and reflex tachycardia may occur. For long-term therapy, extended-release formulations are available which, however, have been widely replaced by long-acting dihydropyridines.	15
Antiarrhythmic drugs				
Amiodarone	14–100 days	p.o., i.v.	Class I–IV antiarrhythmic drug which is effective in the treatment of AF and VT, but cumulates in many organs (liver, lung, nervous system, cornea) where it can cause severe ADRs. Moreover, amiodarone can cause long-term drug interactions by inhibiting CYP2C9 and CYP3A4. Iodine, which is contained in amiodarone, can lead to thyroid gland diseases. Amiodarone is individually administered and requires a high patient adherence.	17, 21
Dronedarone	12 hours	p.o.	Class I–IV antiarrhythmic drug that had been developed to obtain a drug with properties similar to amiodarone, but with improved efficacy and less ADRs. This aim has only been achieved in part. Dronedarone is less effective, and its ADRs and drug interactions (CYP3A4 inhibition) have to be carefully considered.	17

(continued)

Table 2.3 (continued)

Drug	Plasma half-life	Route of application	Pharmacological properties and pharmacotherapeutic consequences	Further contexts in Chaps.
Thyroid hormones				
T3	24 hours	p.o.	Because of the short half-life time of T3, the desired effects (and ADRs) of a T3 therapy are subject to larger fluctuations than those of a T4 therapy. This is why T3 is not appropriate for long-term therapy of hypothyroidism. Because of its rapid onset of action, T3 is only used to manage emergency situations.	21
T4	7 days	p.o.	After p.o. administration, T4 is converted in the body to T3. Because of the long half-life of T4, its pharmacological effect is very constant and well-tolerated by the patient. In takes some time until adjustments in T4 dosage result in desired (and undesired) effects. Because of this favorable pharmacological profile, T4 is the standard drug in the treatment of hypothyroidism.	21
Interferons				
IFN α-2a	4 hours	s.c.	Stimulation of T cells and, thus, of the immune system to respond to viral infections, especially hepatitis C. Traditional IFN injections have to be administered every other day. Variations in drug concentration result in variable antiviral effects. Adherence problems are due to the required long-term therapy (24–48-72 weeks), frequent administration, and ADRs (e.g., influenza, hair loss, weight loss).	34
Peginterferon α-2a	40 hours	s.c.	Coupling of IFN to polyethylene glycol results in protein stabilization and slower degradation. As a result, the drug has to be injected only once a week and the drug effect is more constant. The therapy is less expensive with better adherence.	34

The half-life of a drug must match its intended clinical use

ing to AP and orthostatic hypotension. This pharmacokinetic problem was partially solved by the development of extended-release formulations of nifedipine, but the duration of action was still not sufficiently long. As a consequence, dihydropyridines with a long plasma half-life (12–50 hours) were developed. These long-acting dihydropyridines ensure constant BP decrease and are well suited for long-term therapy of hypertension with only a low incidence of reflex tachycardias.

Pharmacotherapy with thyroid hormones highlights the advantages of a long plasma half-life as well (see ▶ Chap. 21). In the long-term therapy of thyroid gland diseases, exclusively T4 is used because it possesses a long plasma half-life (7 days) and, as a consequence, a very constant effect. This is therapeutically relevant because thyroid hormones modulate the function of virtually every cell type, and fluctuations in thyroid hormone action are uncomfortable for the patient. For this reason, T3, which is the active metabolite of T4 and possesses a much shorter half-life, is not used for chronic treatment. The clinical use of T3 is restricted to the rare but life-threatening hypothyreotic coma in which rapid drug effects are required.

An extremely long plasma half-life can be very problematic. A paradigm for this case is the class

I–IV antiarrhythmic drug amiodarone. In AF and VT, amiodarone shows good clinical efficacy (see ▶ Chapt. 17), but it possesses an extremely long and variable plasma half-life. The long plasma half-life also entails that only after many weeks, steady-state plasma concentrations are reached. In order to avoid this problem, a saturation therapy with initially high drug doses is often performed. Moreover, absorption following oral administration fluctuates, and there are relevant CYP interactions. These properties render individual titration of a patient with amiodarone quite difficult. TDM can partially alleviate this situation. Furthermore, due to its lipophilicity, amiodarone accumulates in many organs (deep compartments) and can cause serious ADRs. Due to its accumulation in organs, amiodarone cannot be eliminated from the organism via dialysis. Therefore, the physician and the patient have to wait for many weeks to months, until the ADRs, if at all, disappear. Because of these problems, dronedarone, an amiodarone-like drug with better pharmacokinetic properties and a greater therapeutic index, was developed. Although dronedarone possesses a much shorter plasma half-life than amiodarone, hopes for greater clinical efficacy of dronedarone were not fulfilled (see ▶ Chap. 17).

In pharmacotherapy, biologicals (recombinantly produced proteins) are of increasing importance. Insulin and insulin analogs are the classic examples of biologicals. Via the specific exchange of single amino acids, the pharmacokinetic properties of insulin are changed in such a way that it is absorbed either rapidly or slowly from the site of injection (subcutaneous fat tissue). As result, insulin possesses either a short or a long duration of action (see ▶ Chap. 19). EPO is another example of a protein in which the duration of action has been varied. By exchanging defined amino acids, the glycosylation pattern of EPO is changed, resulting in delayed degradation and prolonged duration of action (EPO versus darbepoetin) (see ▶ Chap. 12). Another way of stabilizing a protein and prolonging its duration of action in the organism is pegylation, i.e., the attachment of polyethylene glycol (PEG) groups to the protein. IFN-α-2a, which is used in the treatment of hepatitis C, is an example for this concept (see ▶ Chap. 34). IFN-α-2a has to be injected every other day. As a result, both the antiviral effects and ADRs (flu-like symptoms) fluctuate, resulting in adherence problems. As consequence of IFN pegylation, the patient needs to inject the drug less frequently, and the therapeutic effects are more consistent. Moreover, the required drug doses and treatment costs can be reduced.

The duration of action of certain drugs is not determined by their plasma half-life. Mostly drugs that irreversibly modify target proteins belong to this class of drugs. The de novo synthesis of the target protein terminates drug action. The PPIs (see ▶ Chap. 13), irreversibly acting MAOIs (see ▶ Chap. 28), $P2Y_{12}R$ antagonists, and ASA (see ▶ Chap. 18) belong to this class of drugs. ASA (as salicylic acid) possesses a plasma half-life of 2–4 hours, but inhibition of platelet aggregation as a consequence of irreversible COX-1 acetylation lasts up to 1 week. Drugs that exert their effects via NRs and altered gene expression (e.g., thyroid hormones, sex hormones, mineralocorticoids and GCR agonists) possess a much longer duration of action than would be expected from their plasma half-life (see ▶ Chaps. 1, 11, 21, and 24).

2.5 Significance of CYP Inducers and CYP Inhibitors

CYP3A isoenzymes (55% of all drugs), CYP2D6 (30% of all drugs), and CYP2C isoenzymes (10% of all drugs) are the most important enzymes for drug metabolism. Activity of CYP isoenzymes is modulated by drugs, herbal medicines, and food ingredients. In principle, two ways of modifying CYP activity exist. First, a drug can inhibit the activity of one (or more) CYP(s). Secondly, a drug, via NRs (see ▶ Chap. 1), induces the activity of one (or more) CYP(s) and, thereby, increases enzyme activity. CYP induction can already become a problem when a drug induces the activity of the specific CYP that inactivates the drug because this process reduces drug efficacy during long-term therapy. This problem is particularly relevant for antiepileptic therapy (see ▶ Chap. 25). Accordingly, during long-term therapy with a CYP inducer, the drug dose has to be increased in order to ensure a constant therapeutic effect.

Physiologically, CYP induction is a useful mechanism to protect the liver from potentially toxic effects of xenobiotics. Phenytoin, carbamazepine, and phenobarbital (see ▶ Chap. 25) and

the tuberculostatic drug RMP (see ▶ Chap. 33) are drugs that effectively induce CYPs. Additionally, St. John's wort components and nicotine are effective CYP inducer. Classic CYP inhibitors are the azole antimycotics (see ▶ Chap. 35) and the macrolide antibiotics erythromycin and clarithromycin (see ▶ Chap. 33). Moreover, quinolone antibiotics such as ciprofloxacin (see ▶ Chap. 33), the COX-2 inhibitor celecoxib (see ▶ Chap. 10), the SSRIs fluoxetine and paroxetine (see ▶ Chap. 28), the CCB diltiazem and verapamil (see ▶ Chap. 17), and protease inhibitors for HIV and HCV treatment (see ▶ Chap. 34) can inhibit CYP. Furthermore, the bitter substance naringin from grapefruit juice and constituents of goji berries, uncritically advertised as "superfood," inhibit CYPs.

Effects of CYP inducers and CYP inhibitors manifest themselves as drug interactions when the inducer or inhibitor is co-administered with another drug that is metabolized via the same CYP. The interactions are particularly critical when the inducer or inhibitor changes the effects of a drug with small therapeutic index. mGPCR antagonists (see ▶ Chap. 29), the PDE inhibitor theophylline (see ▶ Chap. 14), the VKA phenprocoumon (see ▶ Chap. 18), and the immunosuppressant ciclosporin (see ▶ Chap. 11) are representative drugs with small therapeutic index.

When a patient is treated with two drugs, in general, there is one possibility of CYP-related interaction. However, when a patient takes four different drugs (or two drugs, an herbal medicine and a critical food), there are already at least six possibilities. The number of possible interactions increases exponentially with the number of administered drugs. It is likely that polypharmacy results in ADRs that trigger the prescription of additional drugs to "treat" the ADRs. Therefore, the most important measure to reduce ADRs and the risk of drug interactions is to reduce the number of drugs as far as possible. Discontinuation of drugs, also referred to as deprescribing, quite often improves the health and well-being of a patient. Therefore, every physician and pharmacist is strongly encouraged to critically review the prescription list of a patient suffering from ADRs.

Table 2.4 shows examples of drug interactions of CYP inducers and CYP inhibitors with CYP substrates. It is rather common that psychiatric patients smoke with the goal to stabilize their psychological situation. However, constituents of cigarette smoke can effectively induce CYPs and, thereby, reduce the efficacy of mGPCR antagonists such as clozapine (see ▶ Chap. 29). The loss of efficacy of mGPCR antagonists can, in turn, deteriorate the psychological situation of the patient, triggering increased cigarette smoking. Therefore, psychiatric patients have to be informed about the deleterious consequences of smoking on the effectiveness of psychopharmacological treatment. The physician has also to ensure that the patient actually takes the prescribed medicine. For surveillance of drug effectiveness and adherence, quite often TDM has to be performed.

Many patients with advanced COPD are treated with the bronchodilator theophylline (see ▶ Chap. 14). Theophylline possesses a small therapeutic range and many ADRs that can limit drug therapy. Quite often, patients with COPD get pneumonia. For pneumonia, quinolone antibiotics are commonly prescribed. The prototypical quinolone ciprofloxacin effectively inhibits metabolism of theophylline, thereby augmenting its ADRs. β-Lactam antibiotics which do not inhibit CYPs, therefore, constitute an alternative to ciprofloxacin. For theophylline, TDM and dose adjustment have to be routinely performed. As an alternative, the patient can be treated with the PDE4 inhibitor roflumilast which possesses a higher therapeutic index than theophylline.

Ciclosporin is an immunosuppressant for treatment of autoimmune diseases and prevention of transplant rejection (see ▶ Chap. 11). The therapeutic index of ciclosporin is small as well. Many patients who are treated with ciclosporin also receive GCR agonists for immunosuppression. However, GCR agonists can cause depression (see ▶ Chap. 28). Often, these patients try to treat the depression themselves with St. John's wort extracts, avoiding consultation of a psychiatrist. But most patients are not aware of the fact that these herbal medicines contain potent CYP inducers that accelerate ciclosporin inactivation. Consequently, the immunosuppressant effects of ciclosporin decrease, deteriorating the autoimmune disease or causing transplant rejection. Therefore, all patients receiving ciclosporin have to be informed about the interaction potential of the drug. In any case, to ensure drug efficacy, TDM has to be performed.

Phenprocoumon inhibits vitamin K-dependent carboxylation of coagulation factors in the liver and

Table 2.4 Significance of CYP inhibitors and CYP inducers for drug effects: examples

Drug 1 (CYP substrate)	Active substance 2 and function at CYP	Modified effect of drug 1	Strategy to solve the problem	Further contexts in Chaps.
CYP inducers (active substance 2)				
Ciclosporin, CYP3A4 substrate	St. John's wort, CYP3A4 inducer	Attenuates immunosuppressive effect of ciclosporin; deterioration of autoimmune disease/transplant rejection	The patient has to be informed that certain herbal medicines and ingredients in food and beverages are not as harmless as they seem and can cause severe ADRs due to CYP interactions; discontinue St. John's wort; perform TDM and adjust the dose; switch to other immunosuppressive drugs, if required	11
Clozapine, CYP1A2 substrate	Nicotine, CYP1A2 inducer	Antipsychotic effect is reduced	TDM. The patient has to be informed that tobacco consumption interferes with clozapine treatment; try nicotine withdrawal; adjust the dose; switch to another mGPCR antagonist, if required	5, 28
CYP inhibitors (drug 2)				
Clopidogrel, CYP2C19 substrate	Pantoprazole, CYP2C19 inhibitor	No metabolic activation of clopidogrel and no inhibition of platelet aggregation; higher risk of stent thrombosis, MI and stroke	Check whether pantoprazole medication is required; dose adjustment of clopidogrel based on platelet function testing	18
Haloperidol, CYP2D6 substrate	Celecoxib, CYP2D6 inhibitor	Enhanced ADRs, particularly EPSs or TdP	TDM and dose adjustment; patient has to be informed about possible interactions with other drugs; avoid fast i.v. injection of haloperidol if the patient is "highly agitated" to prevent life-threatening TdP; use biperiden as antidote against EPSs	4, 17, 29
Phenprocoumon, CYP3A4 substrate	Clarithromycin, CYP3A4 inhibitor	Dangerous hemorrhage	In case of emergency, substitution therapy with coagulation factor concentrates. Vitamin K only slowly antagonizes the effect of phenprocoumon; dose adjustment based on INR monitoring; inform the patient about drugs that interfere with phenprocoumon; check patient's medication and discontinue problematic drugs; switch to a DOAC if required; consider higher treatment costs	18

(continued)

Table 2.4 (continued)

Drug 1 (CYP substrate)	Active substance 2 and function at CYP	Modified effect of drug 1	Strategy to solve the problem	Further contexts in Chaps.
Simvastatin, CYP3A4 substrate	Grapefruit juice, CYP3A4 inhibitor	Rhabdomyolysis with myoglobinemia and acute renal failure	Inform the patient about possible drug interactions between simvastatin and ingredients of food and beverages; instruct the patient on initial symptoms of rhabdomyolysis (muscle pain); adjust the dose and avoid other drugs that can cause rhabdomyolysis (e.g., fibrates)	22
Theophylline, CYP1A2 substrate	Ciprofloxacin, CYP1A2 inhibitor	Enhanced ADRs of theophylline (e.g., tachycardia, diarrhea, agitation)	TDM and dose adjustment; replace ciprofloxacin with another effective antibiotic that does not inhibit CYP1A2 (e.g., β-lactam antibiotics, where applicable); replace theophylline with a more specific PDE4 inhibitor (roflumilast), if required	14

Avoid the hazzle of CYP interactions by minimizing the number of drugs that you prescribe

is used for the treatment of thromboembolic diseases (see ▶ Chap. 18). Phenprocoumon is metabolized via CYP3A4 and CYP2C9. As a consequence, there are many opportunities for interactions, either decreased drug effects (risk of thromboembolism) or increased drug effects (risk of hemorrhage). In case that the patient is treated with a macrolide antibiotic because of a respiratory tract infection, CYP3A4 inhibition can result in life-threatening hemorrhage, whereas treatment with CYP3A4 inducers such as NIPEs or St. John's wort can cause thromboembolism. Therapy with phenprocoumon requires information of the patient, good adherence, and monitoring of drug efficacy.

The HMG-CoA reductase inhibitor simvastatin is used for treatment of dyslipidemia (see ▶ Chap. 22). However, when the bioavailability of simvastatin is increased, rhabdomyolysis can occur (see ▶ Sect. 2.2). This serious risk is increased by co-administration of CYP3A4 inhibitors. Macrolide antibiotics, azole antimycotics, and the bitter substance naringin are CYP inhibitors. Therefore, the consumption of grapefruit juice by patients who receive drugs metabolized via CYP3A4 should be avoided.

Clopidogrel is an irreversible $P2Y_{12}R$ antagonist for secondary prevention of MI and stroke (see ▶ Chaps. 16 and 18). In contrast to many other drugs, CYPs do not inactivate but rather activate clopidogrel. Hence, clopidogrel can be considered as a prodrug. Metabolic activation of clopidogrel occurs via CYP2C19. In some patients, the efficacy of clopidogrel is low. Possible reasons are that the patients possess CYP2C19 with low activity (poor metabolizer) or also receive the PPI pantoprazole that inhibits CYP2C19 (see ▶ Chap. 13). Unfortunately, it has become almost a routine practice to prescribe patients receiving a PAI an additional PPI as long-term therapy to "protect the stomach" (see ▶ Chap. 13). However, the long-term use of PPI has to be viewed very critically due to interactions and ADRs, and the use of gastrotoxic COX inhibitors should be avoided.

2.6 Question and Answers

Questions

Which statement on pharmacokinetics is *NOT* correct?

A. Transporters can contribute to resistance against tumor therapeutics.
B. The first-pass effect describes the effect of a drug in the CNS following i.v. injection.
C. A prodrug is the inactive precursor of a drug.

D. The enterohepatic circulation constitutes a cyclic process of secretion of metabolized drugs into the bile and subsequent intestinal absorption.
E. In a zero-order kinetic, a constant amount of drug is administered or eliminated per time interval.

Answers

A. MRPs can export tumor therapeutics from tumor cells. Selection of tumor cells with high MRP activity can render the tumor resistant against a particular drug.
B. The first-pass effect is defined as inactivation of a drug during the first passage through the liver.
C. Prodrugs are used with the goal to increase absorption of a drug in the GI tract or facilitate penetration through the BBB. In general, prodrugs are more lipophilic than the actual drug. Often, prodrugs are esters that are cleaved in the organism by esterases, thereby releasing the active drug.
D. The enterohepatic circulation prolongs the therapeutic effects and ADRs of a drug. In general, the enterohepatic circulation decreases the controllability of pharmacotherapy.
E. I.v. infusion of a drug is an example for zero-order absorption. Oxidation of ethanol by ethanol dehydrogenase in the liver constitutes an example for zero-order elimination.

Statement **B** is not correct.

2.7 Exercises

A 54-year-old patient has been treated for 3 months with a combination of INH + EMB + RMP for TB. Because of a newly diagnosed type 2 DM, the patient is additionally treated with glibenclamide, but despite adherence to an appropriate diet, hyperglycemia is not improved.

Questions

1. How do you explain the therapeutic failure of glibenclamide?
2. Which other pharmacotherapeutic options do you have to treat the type 2 DM?
3. Is the effect of RMP on CYP2C9 induction reversible?

Answers

1. RMP is an effective CYP inducer, e.g., for CYP2C9. Glibenclamide is metabolized via CYP2C9. Thus, increased glibenclamide inactivation is most likely the reason for its lack of effect on DM.
2. Metformin constitutes the first choice for treatment of type 2 DM. This drug is eliminated via the kidneys without metabolism. Therefore, there is no risk for interaction with RMP at the pharmacokinetic level.
3. After termination of the tuberculostatic therapy, CYP induction by RMP will disappear, and the reduced effectiveness of drugs metabolized via CYP1A2, CYP2C9, CYP2C19, CYP2D16, and CYP3A4 normalizes.

Further Reading

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