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REVIEW

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Drug Interactions: A Review

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ABSTRACT

Increased use of drugs as well as polypharmacy has led to increase in incidence of drug interactions. These interactions may lead to medically significant as well as life threatening complications. Not all kind of interactions that can occur with a drug are known. The data in reference safety documents, published literature and safety databases is also limited. Some drugs may also react to certain foods or beverages if taken concomitantly. Most of the interactions come into picture during post-marketing phase of a drug. Latest versions of labelling documents by the manufacturers are informative but not necessarily for newly approved drugs. It is imperative for the healthcare professionals to check for known interactions while prescribing multiple drugs. Detailed diet routine and ongoing medications of subjects also need to be taken into consideration.

KEYWORDS: Drug Interaction, Adverse Drug Reaction, Pharmacokinetics

INTRODUCTION

With increasing polypharmacy and restricted physiological compensation mechanisms in advanced age, the risk of drug interactions and adverse drug reactions naturally increases.[1–3] The clinical significance of drug interactions is indicated by the fact that about 20–30% of the observed adverse effects cannot be attributed to a single medication but are only caused by interactions.[2,3] An intolerable occurrence of interactions that did not occur during the preclinical and clinical development led to market withdrawal for some medications. Even for long-known drugs such as simvastatin and amiodarone, a relevant interaction has only been observed recently. Pharmacokinetic and pharmacodynamic interactions play a significant role in serious adverse drug reactions. The manufacturers' summaries of product characteristics are an important source of information for the physician. In some drugs, the temporal distance from food plays a significant role for the absorption and efficacy of the therapy. Intestinal metabolism is significant for the bioavailability of some drugs and can be influenced by foods such as grapefruit juice. Interactions at this level can lead to extreme changes in bioavailability.

Drug interactions can occur after administration at different levels. At the pharmacokinetic level, release, absorption, distribution, metabolism, and excretion can be impaired by concomitant administration of two or more drugs. At the pharmacodynamic level, similar or contradictory effects can be intensified or reversed at the site of action. The release of a medication depends on its physicochemical properties in connection with the physiological dissolution or release conditions in the gastrointestinal tract. By changing the ambient conditions such as changing the pH value by antacids or proton pump inhibitors, the intestinal motility by metoclopramide or erythromycin, other medicines can therefore impair the release from a formulation.[4] Fiber-containing appetite suppressants and food components can hinder diffusion through increased viscosity and adsorption, and Ca^{2+}, Fe^{2+}, Mg^{2+} and Al^{3+} ions in milk, antacids, and oral iron products can lead to the formation of complexes with tetracycline and fluoroquinolones and thus to a limitation of their efficacy. Penicillin, amoxicillin, and erythromycin are already broken down to an increased extent in the gastrointestinal tract in the case of a prolonged gastric transit time or increased acidity and should therefore be taken on an empty stomach just like isoniazid, levodopa and rifampicin. Furthermore, gastric filling delays gastric emptying depending on the calorie content, which promotes the degradation of acid-sensitive substances such as didanosine, for example. The bioavailability of some drugs like cefuroxime axetil, griseofulvin, danazol, cyclosporine, carbamazepine, spironolactone, phenytoin is significantly improved by fatty meals with prolonged gastric transit time. The cytochrome P450 enzyme system plays a role in intestinal metabolism, especially CYP 3A4. With grapefruit juice, the plasma level of some drugs increases many times over, since flavonoids occurring in grapefruit juice inhibit intestinal CYP 3A4. This in turn results in increased bioavailability of substrates of this enzyme, even if the

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hepatic enzyme CYP 3A4 is evidently not inhibited by these orally administered flavonoids.[5,6] For many interactions at the level of cytochrome P450 enzymes, it cannot be clearly clarified to what extent the pre-systemic or hepatic metabolism is involved in this. However, for some drugs, pre-systemic metabolism appears to be of great importance[6], and if taken with grapefruit juice, significant increases in plasma concentrations up to nine-fold can be observed.

Intestinal membrane efflux pumps, p-glycoprotein (pGP) being the most well-known, have a protective function by discharging foreign substances after absorption from the enterocytes into the intestinal lumen before they enter the systemic blood circulation.[7] Thus, the interaction between calcium antagonists and digitalis glycosides is probably based on the competition for pGP so that the digitalis level increases with this combination. pGP can also be induced by known enzyme inducers such as rifampicin; this reduces the bioavailability of cardiac glycosides and other pGP substrates. An important example of unforeseen, but relevant interaction from induction of the transporter and CYP system is the concomitant administration of Hypericum perforatum and cyclosporine, which leads to a transplant rejection reaction in some patients. Hypericum perforatum induces pGP and some CYP enzymes, in particular CYP 3A4; cyclosporine is thus eliminated increasingly, and plasma concentrations decrease significantly.[8] In this way, digoxin levels also decrease under Hypericum perforatum, the phenprocoumon action is weakened, and, if oral contraceptives are used, intermediate bleeding up to failure of contraception may occur.[9,10]

The extent of distribution of pharmaceuticals at their site of action is determined by the degree of plasma protein binding. In principle, only the free portion of a substance can be released from the capillaries or become effective at the site of action. The occurrence of interactions by mutual displacement from the plasma protein binding had been overestimated for a long time since there are large extracellular "protein buffer capacities" and a very rapid setting of a new equilibrium by rapid elimination and removal of the free-to-release molecules by diffusion. Therefore, the displacement from a binding can only be effective for pharmaceuticals with high plasma protein binding (>90%), small volume of distribution, narrow therapeutic area, and reduced plasma protein binding reserve [11]. In the event of an existing reduction in the plasma protein binding reserve (hypoalbuminemia, hyperproteinemia, tumor, metabolism or edema-related changes in plasma protein content), the sensitivity of this system naturally increases. Possible consequences of displacement reactions with pharmaceuticals with a narrow therapeutic range are bleeding due to increase of a phenprocoumon action, hypoglycemia due to increased sulfonylurea effect, digitoxin-related cardiac arrhythmias, phenytoin-related central disorders, or respiratory depression due to excessive diazepam effect. In addition to a small volume of distribution and high plasma protein binding, the pharmaceuticals listed here also exhibit a slow metabolism and a lack of renal excretion. Caution is advised especially at the start of use of a displacing comedication.

The metabolism of pharmaceuticals takes place mainly in the liver, but sometimes as early as in the intestinal mucosa, and is subdivided into phase I (oxidation, hydroxylation, etc.) and phase II (glucuronidation, sulfation, etc.). Frequently, the summary of product characteristics for new medicinal products lists the cytochrome (CYP) responsible for the phase I metabolism via which a drug is degraded, and possible interactions can be derived from this. Approximately half of the drugs are metabolized via CYP 3A4; approx. 20% are metabolized via CYP 2D6 and CYP 2C8/9/19, respectively. In the process, a mutual influence on concomitant drugs can occur due to inhibition or induction. While the start and end of an induction usually occur with a delay in time of several days, inhibition occurs immediately. However, the latter also persists after discontinuation of the medication until the new synthesis of the respective enzyme in the event of irreversibility (mechanism-based inhibition), e.g. by erythromycin, chloramphenicol, midazolam, verapamil or grapefruit ingredients. In the case of limited enzyme capacity, substrates with strong enzyme binding affinity (low Km) and a higher concentration hereby naturally displace substances with a lower affinity to the metabolizing enzyme from their binding and thus from metabolism. Displacement reactions affecting medicinal substances with narrow therapeutic range (phenprocoumon, digitalis glycosides, theophylline, antiepileptics) are naturally also of special relevance here. Furthermore, the extent of metabolic interactions within a group of drugs is often very different. Thus, each of the selective serotonin reuptake inhibitors (SSRI; e.g. fluoxetine, fluvoxamine, citalopram, sertraline) affects the cytochrome P450 system at another location and to a different extent. Thus, the phenprocoumon metabolism is inhibited by fluvoxamine and there are case reports for fluoxetine regarding the interaction

with warfarin, sertraline showed a small but significant change in prothrombin time for comedication with warfarin, while citalopram and paroxetine do not cause pharmacokinetic interactions with coumarins.

The p-glycoprotein transporter is present both in the intestine and in the liver and in the kidney and is responsible for transport or elimination of numerous drugs (calcium antagonists, digitalis glycosides, cyclosporine). Taking Hypericum perforatum leads to the induction of the p-glycoprotein transporter and a reduction of the efficacy of cyclosporine, phenprocoumon, digoxin and oral contraceptives. Competition for the plasma protein binding only plays a role in drugs with a protein binding of >90%, narrow therapeutic range, and especially at the beginning of the displacing concomitant medication. Many of the known pharmacokinetic interactions are based on the cytochrome P450 enzyme system. Substrates of CYP 3A4, CYP 2D6, CYP 2C9/19 are most commonly affected. Furthermore, the relationship between intestinal absorption and the extent of liver metabolism (first-pass effect) plays a role in the tendency to develop interactions. Simvastatin thus exhibits a high absorption rate (60–80% in animal experimentation) at the same time as low bioavailability (5%), which indicates a high first-pass effect.

In the context of renal excretion of active pharmaceuticals and metabolites, there may be a competition for active tubular secretion mechanisms which inhibit the clearance of one or both interaction partners. Examples include penicillins or NSAID excretion inhibition by probenecid and other organic acids and inhibition of the elimination of sulfonylureas by sulfonamides, otherwise the "baseline" secretion inhibition of metformin, triamterene or zidovudine by cimetidine. An additional renal insufficiency can intensify such an inhibition of secretion and, e.g., in the case of metformin, which is almost exclusively eliminated renally, can trigger lactate acidosis due to a plasma concentration increase. In the meantime, it is known that the already mentioned pGP also plays a role in renal secretion and that some interactions are based on the competition for this transporter. Furthermore, a group of organic anion/cation transporters was identified which are eliminated by many pharmaceuticals. This can lead to interactions with diuretics; one important example for this is comedication with lithium, which is increasingly reabsorbed due to thiazide and (less often) loop diuretics and can easily lead to toxicity through its narrow therapeutic width. In the summary of product characteristics for the antiviral tenofovir, interactions via the human organic anion transporter 1 pointed out in particular. One would need to know in this respect that this is an important transport route for other antiviral substances but also for ß-lactam antibiotics, loop diuretics, and some non-steroidal anti inflammatory drugs.[12]

Pharmacodynamic – meaning action-related – interactions without changing plasma levels can occur at the level of the same receptor or via different mechanisms of action at the same target cell, the same organ or a control circuit. The risk potential of pharmacodynamic interactions can be well estimated by knowledge of the mechanism of action of pharmaceuticals. The antihypertensive therapy through combination of ACE inhibitors and diuretics shows synergistic effects, while NSAID-related prostaglandin inhibition undoes an anti-hypertensive effect or may lead to the above-mentioned worsening of the renal function. More often than one would think, the combination of verapamil or diltiazem with ß-blockers on the one hand or a combination of aforementioned pharmaceuticals with digitalis glycosides on the other hand leads to serious AV blocks or bradycardia. The most common cause for drug induced gastrointestinal bleeding is gastrointestinal bleeding due to comedication with phenprocoumon or acetylsalicylic acid (ASA) with an NSAID. Often, this combination is caused by various prescribers or due to non-prescription pain medication. Dangerous summations of actions, especially in the case of pre-existing genetic disposition, can also be found in the combination of two QT-time prolonging drugs or two substances affecting the metabolism. The interaction between cotrimoxazole or amoxicillin/clavulanic acid and phenprocoumon is based on synergies directly on the coagulation function, decreased vitamin K synthesis by killing the intestinal bacterial flora and probably also on an interaction in the metabolism.[13] The relevance of an interaction is influenced by, among other things, how high the absorption rate of a drug is and to what extent the affected drug is subject to a first-pass metabolism. In the case of a high absorption rate and pronounced first pass, a tenfold increase of the systemic bioavailability can be induced by the inhibition of the first pass within the context of an interaction. In the kidney, organic and inorganic transporters and the pGP are responsible for secretion and elimination. Competitive displacement can also

occur here.

An information source for relevant interactions, both of pharmacokinetic and pharmacodynamic nature, is the so called summaries of product characteristics of the manufacturers, which are considerably more informative than the information uploaded online. However, when using these summaries of product characteristics, it is necessary to know that, although they are regularly updated, they cannot yet be complete for newly approved drugs. In the case of new substances from an already known group (e.g. proton pump inhibitors), the interactions of the substances already on the market can certainly be mentioned without ever having been proven for the new medication. Interaction information with coumarin is often based on unproven parallel conclusions. Most studies in this regard were conducted with warfarin, which is subject to a different metabolism than the phenprocoumon and therefore cannot necessarily be transferred to this substance. The summaries of product characteristics often also do not indicate whether an interaction is a interaction specifically investigated in the context of a clinical study or whether more-or-less well documented individual case reports have led to the inclusion of this note. Thus, the warning that ß-blockers suppress the hypoglycemia symptoms in diabetics under antidiabetic therapy should not lead to the discontinuation of ß-blockers in patients with diabetes mellitus, since the benefit is documented in terms of clinically relevant endpoints.
Pharmacodynamic interactions result from the pharmacological profile of the individual substances and are usually predictable. They are often not observed due to their apparent triviality. Some pharmacodynamic interactions manifest only in a few, probably genetically predisposed patients e.g. drug induced torsade de pointes arrhythmia or rhabdomyolysis under statins and fibrates. The basis for information regarding interactions in the product information provided by manufacturers is very heterogeneous. They are partially based on clinical studies but are frequently only based on individual case reports.

Drug-drug and drug-meal interactions are of clinical concern for prescribed drugs. Drug interactions contribute to a major part of adverse drug reactions, especially in elderly patients and in patients under polymedication.

CONCLUSION

Numerous drug reactions can be prevented if physicians respond early to the symptoms reported by patients. The number of more frequent and clinically relevant interactions is limited. It can be reduced further by restriction to a few and known drugs. In the case of new prescriptions, especially in the case of rarer or less well-known medicinal products, interactions should always be looked out for. Patients should be encouraged to maintain vigilance and motivated to communicate abnormalities. The use of electronic tools for early detection of potential interactions can only be useful when using validated and clinically relevant information. The vigilance and cooperation of the patient are indispensable.

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