

Pharmacokinetic drug-drug interaction and their implication in clinical management

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Drug-drug interactions (DDIs) are one of the commonest causes of medication error in developed countries, particularly in the elderly due to poly-therapy, with a prevalence of 20-40%. In particular, poly-therapy increases the complexity of therapeutic management and thereby the risk of clinically important DDIs, which can both induce the development of adverse drug reactions or reduce the clinical efficacy. DDIs can be classified into two main groups: pharmacokinetic and pharmacodynamic. In this review, using Medline, PubMed, Embase, Cochrane library and Reference lists we searched articles published until June 30 2012, and we described the mechanism of pharmacokinetic DDIs focusing the interest on their clinical implications.

Key words: Absorption, adverse drug reaction, distribution, drug-drug interactions, excretion, metabolism, poly-therapy

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INTRODUCTION

Pharmacovigilance or post-marketing surveillance aims to identify and quantify the risks associated with the use of drugs, thus contributing to better understand the most important characteristics of adverse drug reactions (ADRs) and the pathogenic mechanisms involved.^[1] Indeed, ADRs represent a common clinical problem and can be responsible for an increased number and/or duration of hospitalizations.^[2,3]

Drug-drug interactions (DDIs) are one of the commonest causes of ADRs and we reported that these manifestations are common in the elderly due to poly-therapy.^[4-7] In fact, poly-therapy increases the complexity of therapeutic management and thereby the risk of clinically relevant drug interactions, which can induce the development of ADRs, and both reduce,^[8,9] or increase the clinical efficacy.^[10,11]

Poly-therapy may determine the “prescribing cascade,” which occurs when an ADR is misunderstood and new potentially unnecessary drugs are administered; therefore the patient is at risk to develop further ADRs.^[12]

DDI can be classified into two main groups:

- Pharmacokinetic: Involves absorption, distribution, metabolism and excretion, all of them being

associated with both treatment failure or toxicity;

- Pharmacodynamic: may be divided into three subgroups: (1) direct effect at receptor function, (2) interference with a biological or physiological control process and (3) additive/opposed pharmacological effect.

In this review, we described the mechanism of pharmacokinetic DDI focusing the interest on their clinical implications, addressing the reader’s attention for pharmaceutical interactions to other original and review articles.

METHODS

Medline, PubMed, Embase, Cochrane library and Reference lists were searched for articles published until June 30 2012, using the words “ADR,” “drug interactions,” “polytherapy,” “elderly.”

Pharmacokinetic DDI

Pharmacokinetic interactions are often considered on the basis of knowledge of each drug and are identified by controlling the patient’s clinical manifestations as well as the changes in serum drug concentrations. As above reported, they involved all the processes from absorption up to excretion that will be now described.

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Absorption

Gastro-intestinal absorption

The complexity of the gastro-intestinal tract, and the effects of several drugs with functional activity on the digestive system, represent favourable conditions for the emergence of DDI that may alter the drug bioavailability.^[13]

Several factors may influence the absorption of a drug through the gastrointestinal mucosa. The first factor is the change in gastric pH. The majority of drugs orally administered requires, to be dissolved and absorbed, a gastric pH between 2.5 and 3. Therefore, drugs able to increase gastric pH (i.e., antacids, anticholinergics, proton pump inhibitors [PPI] or H₂-antagonists) can change the kinetics of other co-administered drugs.

In fact, H₂ antagonists (e.g., ranitidine), antacids (e.g., aluminium hydroxide and sodium bicarbonate) and PPI (e.g., omeprazole, esomeprazole, pantoprazole) that increase the gastric pH lead to a decrease in cefpodoxime bioavailability, but on the other hand, facilitate the absorption of beta-blockers and tolbutamide.

Moreover, antifungal agents (e.g., ketoconazole or itraconazole), requires an acidic environment for being properly dissolved, therefore, their co-administration with drugs able to increase gastric pH, may cause a decrease in both dissolution and absorption of antifungal drugs.^[14] Therefore, antacid or anticholinergics, or PPI might be administered at least 2 h after the administration of antifungal agents.^[15]

Similarly, the administration of drugs able to increase the gastric pH (see above) with ampicillin, atazanavir, clopidogrel, diazepam, methotrexate, vitamin B12, paroxetine and raltegravir are not recommended.

In contrast, the ingestion of drugs that cause a decrease in gastric pH (e.g., pentagastrin), may have an opposite effect. It is worth noting that severity of DDIs caused by alteration of gastric pH mainly depends on pharmacodynamics characteristics of the involved drug, in terms of narrow therapeutic range.

Another factor that modifies the drug absorption is the formation of complexes. In this case, tetracyclines (e.g., doxycycline or minocycline) in the digestive tract can combine with metal ions (e.g., calcium, magnesium, aluminum, iron) to form complexes poorly absorbed. Consequently certain drugs (e.g., antacids, preparations containing magnesium salts, aluminum and calcium preparations containing iron) can significantly reduce the tetracyclines absorption.^[16] Analogously, antacids reduce the absorption of fluoroquinolones (e.g., ciprofloxacin),

penicillamines and tetracyclines, because the metal ions form complexes with the drug. In agreement, was observed that antacids and fluoroquinolones should be administered at least 2 h apart or more.^[17,18]

Cholestyramine and colestipol bind bile acids and prevent their absorption in the digestive tract,^[19] but they can also bind other drugs, especially acidic drugs (e.g., warfarin, acetylsalicylic acid, sulfonamides, phenytoin, and furosemide). Therefore, the interval between the administration of cholestyramine or colestipol and other drugs may be as long as possible (preferably 4 h).^[20]

Motility disorders represent the third factor involved in absorption DDIs. Drugs able to increase the gastric transit (e.g., metoclopramide, cisapride or cathartic) can reduce the time of contact between drug and mucosal area of absorption inducing a decrease of drug absorption (e.g., controlled-release preparations or entero-protected drugs).^[21]

For example, metoclopramide, may accelerate gastric emptying, hence decreasing the absorption of digoxin and theophylline whereas it can accelerate the absorption of alcohol, acetylsalicylic acid, acetaminophen, tetracycline and levo-dopa.^[22]

Finally, iron can inhibits the absorption of levodopa and metildopa.

Modulation of P-glycoprotein (P-gp) intestinal

P-gp or gp-120 for its molecular weight, is a transmembrane protein encoded by the human multidrug resistance gene-1 belonging to the adenosine triphosphate-binding cassette (ABC) superfamily, together with other 41 members grouped in 7 families (A to G).^[23] Localized in liver, pancreas, kidney, small and large intestine, adrenal cortex, testes and leukocytes, P-gp plays a protective role influencing the trans membrane drugs diffusion thus reducing their absorption or increasing their excretion or limiting their tissues distribution (i.e., central nervous system, foetal and gonadic tissues).^[24]

P-gp regulates the intestinal absorption of drugs (it is present on the luminal surface of enterocytes) and promotes their excretion (it is present on the side tubular of epithelium renal and biliary side of hepatocytes). Therefore, the administration of drugs able to stimulate to inhibit the activity of P-gp, can induce the development of DDI.

The P-gp inhibition can significantly increase the bioavailability of drugs poorly absorbed.^[25]

Among the interactions studied at the time of this review, it is worth mentioning the effects of terfenadine

on the transport of doxorubicin as well as the effects chlorpromazine and progesterone on the transport of cyclosporine.^[26] The DDIs on P-gp might induce a clinical effect in presence of drugs with a low therapeutic index (e.g., digoxin, theophylline, anticancer drugs) when co-administered with macrolides (e.g., erythromycin, roxithromycin, clarithromycin), PPIs (e.g., omeprazole or esomeprazole) or anti-arrhythmic drugs (e.g., dronedarone, amiodarone, verapamil or diltiazem).

Many drugs (but not all) that are transported by P-gp are also metabolized by cytochrome P450 (CYP) isoform 3A4 (e.g., cyclosporine, antiepileptic drugs, antidepressant, fluoroquinolones, quinidine and ranitidine), which can confound interpretation of interactions (see later).

Therefore, the co-administration of these drugs with known inhibitors of P-gp above described results in a clinically evident DDI.

Recently, it has been described that aripiprazole and its active metabolite, dehydroaripiprazole, but not risperidone, paliperidone, olanzapine and ziprasidone are strong P-gp inhibitors, *in vitro*, while *in vivo* their administration is unlikely to induce DDIs at the blood-brain-barrier, but the possibility of DDIs in the intestine cannot be neglected.

However, it is important to underline that a DDI could be also used in clinical management. In fact, Shi *et al.*^[27] documented that sildenafil inhibits the transporter function of P-gp, suggesting a possible strategy to enhance the distribution and potentially the activity of anticancer drugs.

DISTRIBUTION

Usually, drugs are transported through a binding to plasma and tissues proteins. Of the many plasma proteins interacting with drugs, the most important are albumin, α_1 -acid glycoprotein, and lipoproteins. Acidic drugs are usually bound more extensively to albumin, while basic drugs are usually bound more extensively to α_1 -acid glycoprotein, lipoproteins, or both. Only unbound drug is available for passive diffusion to extravascular or tissue sites and typically determines drug concentration at the active site and thus its efficacy. Albumin represents the most prominent protein in plasma, it is synthesized in the liver and distributed in both plasma and extracellular fluids of skin, muscles and various tissues. Intestinal fluid albumin concentration is about 60% of that in the plasma. Since albumin has five binding sites (i.e., for warfarin, benzodiazepines, digoxin, bilirubin and tomozifen), the main characterized are the site I and II.^[28]

Site I, also known as the warfarin binding site, is formed

by a pocket in subdomain IIA,^[29] while site II located in subdomain IIIA is known as the benzodiazepine-binding site. Ibuprofen and diazepam are selective drug probes for site II.^[29-31] [Table 1]

As the free molecules interact with their molecular targets and are metabolized, other molecules come into solution to reach the site of action. The degree of plasma protein binding, expressed by the ratio of bound drug concentration/free drug concentration, varies greatly among drugs, possibly reaching very high values, especially when it is greater than 0.9, otherwise it is considered to be low (<0.2). Drugs that have a high degree of plasma protein binding are potentially more likely to be displaced by drug with greater affinity for the same binding site. From a mere clinical point of view, that displacement could be associated with symptoms, side effects or toxicities when the displaced drug has a higher degree of binding to plasma proteins (>90%), reduced volume of distribution, narrow therapeutic index, and it is characterized by a faster onset of the effect

A typical pharmacological displacement can be observed when warfarin and diclofenac are co-administered. Warfarin and diclofenac have same affinity for albumin, therefore the administration of diclofenac to a patient treated chronically with warfarin results in displacement of latter from its binding site. The increase in plasma concentration of free warfarin causes the development of serious hemorrhagic reactions.

Metabolism

The CYP enzyme family plays a dominant role in the biotransformation of a wide number of drugs. In man, there are about 30 CYP isoforms, which are responsible for drug metabolism and these belong to families 1-4, but only 6 out of 30 isoforms belonging to families CYP1, 2 and 3 (i.e., CYP1A2, 3A4, 2C9, 2C19, 2D6 and 2E1) are mainly involved in the hepatic drug metabolism.^[32-35]

Table 1: Drugs binding to site I (warfarin) or II (benzodiazepines) of albumin

Site I (warfarin)	Site II (benzodiazepines)
Chlorothiazide	Ketoprofen
Phenytoin	Ibuprofen
Glibenclamide	Indomethacin
Naproxen	Dicloxacilline
Salicylates	Nimesulide
Nimesulide	
Diclofenac	
Sulphamidics	
Fluoroquinolones	
Valproate	

The broad range of drugs that undergo CYP mediated oxidative biotransformation is responsible for the large number of clinically significant drug interactions during multiple drug therapy. Many DDIs are related to the inhibition or induction of CYP enzymes.

Inhibition

Inhibition-based DDIs constitute the major proportion of clinically relevant DDIs. In this process enzyme activity is reduced due to direct interaction with a drug, usually begins with the first dose of the inhibitor, while the extinction of inhibition is related to the drug half-lives.^[36,37]

The metabolic inhibition may be reversible (competitive, metabolic-intermediate complex, non-competitive) or irreversible, and clinical effects are influenced by basic mechanisms.

Reversible inhibition

Competitive

The competitive inhibition occurs when inhibitor and substrate compete for the same binding site on the enzyme. In this type of interaction, the inhibition mechanism is direct and is rapidly reversible.

The drugs are converted through multiple CYP dependent steps to nitroso-derivatives that bind with high affinity to the reduced form of CYP enzymes. Thus CYP enzymes are unavailable for further oxidation and synthesis of new enzymes is therefore, the only means by, which activity can be restored and this may take several days.^[38]

It depends on the substrate-versus-inhibitor binding constant ratio, and on the relative concentrations of each species. Some of the inhibitors of CYP3A4 that act by this mechanism of inhibition include azole antifungal agents, some HIV protease inhibitors such as nelfinavir mesylate,^[39] and antihypertensives such as diltiazem.^[40] In particular, it has been reported a two-fold decrease in oral clearance of metoprolol in presence of propafenone; therefore, during a co-administration the dose of metoprolol should be reduced.^[41]

However, recently we reported a case of an 85-year-old woman that developed visual hallucinations and psychomotor agitation during the treatment with venlafaxine and propafenone.^[42] We postulated a DDI between venlafaxine and propafenone because venlafaxine is metabolized primarily by CYP2D6 and is a substrate of P-gp, while propafenone is a known substrate and inhibitor of both CYP2D6 and P-gp. Therefore, propafenone may be induced an increase of venlafaxine plasma concentrations with the development of hallucinations.

Similar DDI are seen in the combined administration of thioridazine and propranolol (CYP2D6),^[43] fluoxetine and desipramine (CYP2D6),^[44] omeprazole and diazepam (CYP2C19),^[45-47] tolbutamide and phenytoin (CYP2C9),^[48] and diltiazem and cyclosporin (CYP3A).^[49-51]

Omeprazole, a CYP2C19 inhibitor, decreases the antiplatelet activity of clopidogrel by inhibiting the biotransformation of the clopidogrel pro drug into its active metabolite.^[52] In patients hospitalized for acute coronary syndrome, this interaction is associated with a 27% increased risk of death or re-hospitalization.^[53] By analogy, inhibition of CYP2C19 by etravirine may also inhibit clopidogrel antiplatelet activity. Until more data become available, the co-administration of CYP2C19 inhibitors (e.g., etravirine and omeprazole) and clopidogrel is not recommended.

Moreover, omeprazole treatment should be well evaluated in elderly patients due the possibility to induce the development of ADR. In fact, previously we reported in an elderly man the development of delirium probably related to a DDI between omeprazole and amitriptyline through the CYP2C19 inhibition.^[54]

Amiodarone is metabolized by CYP3A4 and 2C8; *in vitro* is an inhibitor of CYP3A4, 1A2, 2C9 and 2D6. Due to its long half-life (about 30 days), the risk of interaction must be extended also at the period after the treatment with amiodarone. However, the risk of interactions may also depend on its main metabolite, desethylamiodarone, a competitive inhibitor of CYP2D6, an irreversible inhibitor of CYP2A6, 3A4, and 2B6 (for formation of covalent bond), a mixed inhibitor of CYP1A1, 1A2, 2C9 and 2C19.^[55]

Similarly, HIV protease inhibitors (i.e., saquinavir and ritonavir) increase sildenafil serum concentrations up to 11-fold.^[56] Similarly, it has been recently reported that azole antifungal drugs (i.e., ketoconazole, itraconazole, voriconazole and posaconazole) are CYP3A inhibitors able to induce DDIs.^[57] In particular posaconazole exhibit inhibitory effects upon CYP3A and PGP and at the dosage of 200 mg for 10 days can able to reduce from 1.2 to 1.5 fold the steady-state clearance of cyclosporine. Moreover, in an open-label study performed in 36 healthy volunteers, the treatment with posaconazole (400 mg twice daily) for 14 days increased the plasma concentrations of tacrolimus of 2.2-fold, the area under the curve (AUC) of 4.5-fold, and the half-life up to 7.5 h.^[58] Therefore, the dosage of tacrolimus should be reduced up to 66% of the original dose, in presence of posaconazole. Similar DDI have been documented when azole antifungal treatment was administered in patients taking sirolimus or everolimus, therefore, an empiric dose reductions of 50% may be considered for both sirolimus and everolimus.

However, in a single-centre study enrolling 20 healthy subjects, Kapil *et al.*,^[59] documented the lack of a clinically significant CYP3A4 interaction between ketoconazole and transdermal delivery of buprenorphine. It is consistent with the parenteral administration of a high clearance drug bypassing exposure to gut wall and hepatic CYP3A4 first-pass effects.

Metabolic-intermediate complexes

The production of metabolic-intermediate complexes is an unusual form of inhibition where the inhibitor binds only to the enzyme-substrate complex. The formation of a metabolic-intermediate complex results from inhibitors that have an N-alkyl substituent. After the binding of inhibitor, the latter is oxidized by 3A4 and the resultant oxidized species of the inhibitor remains complexed with the reduced heme group of CYP3A4 forming a complex slowly reversible. Erythromycin is a well-known CYP3A4 inhibitor that uses this mechanism of inhibition,^[60] whereas clarithromycin displays reduced inhibitory effects with a good clinical efficacy.^[61]

Non-competitive

In the non-competitive mechanism, the inhibitor and substrate do not compete for the same active site, because the presence of an allosteric site. Once a ligand binds the allosteric site the conformation of the active site changes, its ability to bind the substrate decreases and the product formation tails off. Many drugs are non-competitive inhibitors of CYP isoforms, as well as omeprazole and lansoprazole, and cimetidine.^[62,63] The duration of this type of inhibition may be longer if new enzymes have to be synthesized after the inhibitor drug is discontinued.

Irreversible inhibition

The metabolite resulting from the oxidation of the substrate by CYP3A4 becomes irreversible and covalently bound to 3A4, thus leading to a permanent inhibition of the enzyme. In the case of irreversible inhibition the critical factor is represented by the total amount rather than the concentration of the inhibitor to which CYP isoenzyme is exposed. Lipophilic and large molecular size drugs are more likely to cause inhibition.^[25] Two characteristics make a drug susceptible to inhibitory interactions: one metabolite must account for >30-40% metabolism of a drug and that metabolic pathway is catalyzed by a single isoenzyme.^[48]

Inhibitor will decrease the metabolism of substrate and generally lead to increased drug effect or toxicity of the substrate. If the drug is a pro drug the effect is decreased.

Garraffo *et al.* investigated in an open-label study the effects of single-dose administration and steady-state concentrations of tipranavir 500 mg and ritonavir 200 mg combination on the pharmacokinetics of tadalafil 10 mg.^[64]

The authors documented that even if antiretroviral activity of both tipranavir and ritonavir may not be reduced, the dose of tadalafil should be reduced at the start of antiretroviral therapy and then a full dose can be resumed after steady state is reached.

The co-administration of 3A4 inhibitors with the hydroxymethylglutaryl-coenzyme A reductase inhibitors (statins; e.g., simvastatin) could increase the risk of myopathy^[65] and rhabdomyolysis.^[66] However, it is important to understand that during the treatment with statins it is possible the development of myopathy also for metabolic saturation, in particular during the poly-therapy.^[67]

Metabolic induction

Drug interactions involving enzyme induction are not as common as inhibition-based drug interactions but equally profound and clinically important. Exposure to environmental pollutants as well as the large number of lipophilic drugs can result in induction of CYP enzymes. The most common mechanism is transcriptional activation leading to increased synthesis of more CYP enzyme proteins.^[61] The effect of induction is simply to increase the amount of P450 present and speed up the oxidation and clearance of a drug.^[43]

The most common enzyme inducers are rifampicin,^[68-76] phenobarbital,^[76,77] phenytoin,^[77,78] carbamazepine,^[78-80] and anti-tubercular drugs.^[79]

Rifampicin induces CYP3A enzymes in the liver, although weak induction of other CYP enzymes, including, CYP2A6, CYP2C and CYP2B6, have also been noticed. Rifampicin increases the elimination of a large number of drugs, although most of them are substrates for CYP3A4, such as midazolam, quinidine, cyclosporine A and many steroids.

Metabolism of the affected drug is increased leading to decreased intensity and duration of drug effects.^[81] It is rather difficult to predict the time-course of enzyme induction because of several factors, including the half-life and the enzyme turnover, which determine the time-course of induction. A complicating factor is that the time-course of induction depends on the time required for enzyme degradation and new enzyme production.

The short half-life of rifampicin results in enzyme induction (CYP3A4, CYP2C), apparent within 24 h, whereas phenobarbital, which has a half-life of 3-5 days, requires approximately 1 week for induction (CYP3A4, CYP1A2, CYP2C) to become apparent. These enzyme-induction reactions also occur with smoking and long-term alcohol or drug consumption and can reduce the duration of action of a drug by increasing its metabolic elimination.

Recently, we documented in a patient with epilepsy a DDI between phenobarbital and lamotrigine that induced the development of leukopenia and thrombocytopenia. We postulated that CYP enzyme induction by phenobarbital could be responsible for the production of reactive metabolites of lamotrigine that might be causative for the observed hematologic effects.^[82]

DDIs during excretion

The organs and vehicles deputy at the drugs excretion (elimination) are kidneys, liver, lungs, feces, sweat, saliva, milk. The excretion through saliva, sweat and lungs (for volatile drugs) and milk has little quantitative significance, but the milk is important when the drugs can reach the baby during lactation.

Drugs are excreted mainly through:

- Renal tubular excretion (glomerular filtration, tubular reabsorption and active tubular secretion)
- Biliary excretion.^[83]

The drugs elimination from the body can undergo many interactions being excreted by another drug in this organ from, which it is excreted.^[84]

The kidney is the organ responsible for the elimination of drugs and their metabolites. The interaction may occur for a mechanism of competition at the level of active tubular secretion, where two or more drugs use the same transport system. An example is given by NSAIDs that determine the appearance of toxic effects caused by methotrexate when the renal excretion of the anti-proliferative drug is blocked.^[85]

It was also demonstrated that amoxicillin decreased the renal clearance of methotrexate.^[86]

Probenecid, a potent inhibitor of the anionic pathway of renal tubular secretion, increases of 2.5 times the area under the AUC of oseltamivir.^[87]

However, this competition between drugs can be exploited for therapeutic purposes. For example, probenecid can increase the serum concentration of penicillins and cephalosporins, delaying their renal excretion and thus saving in terms of dosage. In fact, probenecid acts by competitively inhibiting an organic anion transporter in renal tubules, thus increasing plasma concentrations of other transporter substrates, while reducing their excretion.^[88]

Several drugs are able to interfere with tubular transport. In particular, cimetidine, an H₂ receptor inhibitor, may influence the tubular secretion of different molecules. Its effect on the influx and the efflux of organic cations through

human organic cation transporter ([hOCT1 and hOCT2] and human multidrug and toxin extrusion [hMATE1 and hMATE2-K]) could modify other drug serum concentration despite a normal renal function.^[89]

Moreover, *in vitro* study documented that PPIs (i.e., omeprazole, pantoprazole, lansoprazole, rabeprazole, and tenatoprazole) are potent hOCT-inhibitors and could modulate the transport of metformin.^[90] However, the clinical relevance of this DDIs may be clarify. The interactions can also occur during tubular reabsorption. Many drugs, when they are in an ionized form in the urine, pass by diffusion in tubular cells. The changes in urinary pH, pharmacologically induced, influence the state of ionization of certain drugs and may therefore affect the re-absorption from the renal tubule.^[91]

In particular, if the pH of the urine is alkaline the absorption of acidic drugs is reduced, while, in the presence of an acidic pH, basic drug absorption is reduced.

The changes in urinary pH, however, assume practical importance only if the pKa of the drug, i.e., the pH at which 50% of the molecules in solution is present in ionized form, is between 7.5 and 10.5 for the bases, and between 3.0 and 7.5 for acids.

In fact, the pKa values can cause appreciable changes in the degree of dissociation of the drug. Compounds such as ammonium chloride, tromethamine and diuretics, being able to change urine pH, may affect the excretion of several acidic and basic drugs,^[15] and this interaction may be used to facilitate the removal of drugs from the body. On the contrary, the interaction between diuretics and lithium salts can still have negative effects on the patient.

Lithium is a monovalent cation whose excretion is influenced by changes of serum sodium. Therefore, a high excretion of sodium induced by chronic treatment with some diuretics such as thiazides, may increase lithium re-absorption, causing serious toxic effects from relative over dosage.^[92,93]

Some acidic and basic drugs with the high degree of ionization are transferred through the epithelium of the renal tubule by active transport. The speed transfer of molecules depends on the availability of the transporter, a protein that allows the transfer through the cellular membranes. Therefore, when two drugs are substrate of the same transmembrane transporter they can complete each other, up to the saturation of transporter capacity. At that time, the rate of elimination approaches to a zero order (saturable) process.

Strategy to prevent pharmacokinetic DDI

The Summary of Product Characteristics (SPCs) represents the primary source of information about DDIs for health care professionals. Unfortunately, DDI cannot be listed exhaustively. Consequently the information on potential DDIs may be insufficiently described, due to the limited space in the SPC.

In fact, in an Italian study cross-sectional study, was found that the 3.0% of PPI users were exposed to potential DDI within 1 year of follow-up, according to the risk described in the Italian SPCs of PPIs, but this proportion was three-fold higher (9.0%) when information about DDI risk with PPIs, reported on Drugdex, was considered.^[94]

Therefore, reports on DDI that consider different sources updated on the basis of current evidence from the literature should be useful to evaluate a possible risk of DDI particularly in elderly patients with poly-therapy.

Moreover, even if not always available and feasible, the adoption of therapeutic drug monitoring protocols in the above reported patients (i.e., elderly people with comorbidities treated with multiple drugs) should be considered an important instrument to decrease the occurrence and magnitude of DDIs that could induce either an increase in health costs for the Health system and a legal responsibility for the clinicians.

Therefore, we hope that the National Health System plan a strategy intervention to keep physicians adequately aware of potential DDI, with particular regard to widely used medications.

However, in this time, reports on DDIs that consider different sources updated on the basis of current evidence from the literature should be useful to evaluate a possible risk of DDI particularly in elderly patients with poly-therapy.

Previously it has been reported that genetic polymorphism of CYP enzymes played a significant role in the clinical effects of drug treatment^[7,95,96] as well as in the development of DDIs.^[97]

In this light, even if not always available and feasible, both the adoption of therapeutic drug monitoring in patients with multiple drug treatment and *in vitro* techniques to predict the role of CYP enzymes polymorphism in DDIs, should be considered an important instrument to decrease the occurrence and magnitude of DDIs.

CONCLUSIONS

DDIs represent a common clinical problem during the management of patients treated with several drugs.

However, may be underlined that only two drugs are able to induce the development of a DDI even if this clinical relevance is related to the pharmacology of each drug. In fact, a DDI will be able to induce a clinically relevant effect in presence of drugs with a low therapeutic index, a long half-life and a higher bound with plasma proteins.

Moreover, it is important to underline that the development of DDI is not a problem a class of drug but of a single drug and this problem could be under estimated considering the SPC only.

REFERENCES

1. Moore N, Biour M, Paux G, Loupi E, Begaud B, Boismare F, *et al.* Adverse drug reaction monitoring: Doing it the French way. *Lancet* 1985;2:1056-8.
2. Lee CE, Zembower TR, Fotis MA, Postelnick MJ, Greenberger PA, Peterson LR, *et al.* The incidence of antimicrobial allergies in hospitalized patients: Implications regarding prescribing patterns and emerging bacterial resistance. *Arch Intern Med* 2000;160:2819-22.
3. Bordet R, Gautier S, Le Louet H, Dupuis B, Caron J. Analysis of the direct cost of adverse drug reactions in hospitalised patients. *Eur J Clin Pharmacol* 2001;56:935-41.
4. Gallelli L, Ferreri G, Colosimo M, Pirritano D, Guadagnino L, Pelaia G, *et al.* Adverse drug reactions to antibiotics observed in two pulmonology divisions of catanzaro, Italy: A six-year retrospective study. *Pharmacol Res* 2002;46:395-400.
5. Gallelli L, Ferreri G, Colosimo M, Pirritano D, Flocco MA, Pelaia G, *et al.* Retrospective analysis of adverse drug reactions to bronchodilators observed in two pulmonary divisions of Catanzaro, Italy. *Pharmacol Res* 2003;47:493-9.
6. Gallelli L, Colosimo M, Pirritano D, Ferraro M, De Fazio S, Marigliano NM, *et al.* Retrospective evaluation of adverse drug reactions induced by nonsteroidal anti-inflammatory drugs. *Clin Drug Investig* 2007;27:115-22.
7. Gallelli L, Colosimo M, Tolotta GA, Falcone D, Luberto L, Curto LS, *et al.* Prospective randomized double-blind trial of racecadotril compared with loperamide in elderly people with gastroenteritis living in nursing homes. *Eur J Clin Pharmacol* 2010;66:137-44.
8. Franceschi A, Tuccori M, Bocci G, Vannozzi F, Di Paolo A, Barbara C, *et al.* Drug therapeutic failures in emergency department patients. A university hospital experience. *Pharmacol Res* 2004;49:85-91.
9. Johnell K, Klarin I. The relationship between number of drugs and potential drug-drug interactions in the elderly: A study of over 600,000 elderly patients from the Swedish Prescribed Drug Register. *Drug Saf* 2007;30:911-8.
10. Siniscalchi A, Gallelli L, Avenoso T, Squillace A, De Sarro G. Effects of carbamazepine/oxycodone coadministration in the treatment of trigeminal neuralgia. *Ann Pharmacother* 2011;45:e33.
11. Canu B, Fioravanti A, Orlandi P, Di Desidero T, Ali G, Fontanini G, *et al.* Irinotecan synergistically enhances the antiproliferative and proapoptotic effects of axitinib *in vitro* and improves its anticancer activity *in vivo*. *Neoplasia* 2011;13:217-29.
12. Rochon PA, Gurwitz JH. Optimising drug treatment for elderly people: The prescribing cascade. *BMJ* 1997;315:1096-9.
13. Mantia G, Provenzano G. Rilevanza clinica delle interazioni farmacologiche di tipo farmacocinetico. *Acta Medica Mediterr* 2008;24:23-27.

14. Krishna G, Moton A, Ma L, Medlock MM, McLeod J. Pharmacokinetics and absorption of posaconazole oral suspension under various gastric conditions in healthy volunteers. *Antimicrob Agents Chemother* 2009;53:958-66.
15. Ogawa R, Echizen H. Drug-drug interaction profiles of proton pump inhibitors. *Clin Pharmacokinet* 2010;49:509-33.
16. Bokor-Bratić M, Brkanić T. Clinical use of tetracyclines in the treatment of periodontal diseases. *Med Pregl* 2000;53:266-71.
17. Ogawa R, Echizen H. Clinically significant drug interactions with antacids: An update. *Drugs* 2011;71:1839-64.
18. Seedher N, Agarwal P. Effect of metal ions on some pharmacologically relevant interactions involving fluoroquinolone antibiotics. *Drug Metabol Drug Interact* 2010;25:17-24.
19. Scaldaferrri F, Pizzoferrato M, Ponziani FR, Gasbarrini G, Gasbarrini A. Use and indications of cholestyramine and bile acid sequestrants. *Intern Emerg Med* 2011;8.
20. Phillips WA, Ratchford JM, Schultz JR. Effects of colestipol hydrochloride on drug absorption in the rat II. *J Pharm Sci* 1976;65:1285-91.
21. Lee HT, Lee YJ, Chung SJ, Shim CK. Effect of prokinetic agents, cisapride and metoclopramide, on the bioavailability in humans and intestinal permeability in rats of ranitidine, and intestinal charcoal transit in rats. *Res Commun Mol Pathol Pharmacol* 2000;108:311-23.
22. Johnson BF, Bustrack JA, Urbach DR, Hull JH, Marwaha R. Effect of metoclopramide on digoxin absorption from tablets and capsules. *Clin Pharmacol Ther* 1984;36:724-30.
23. Wynn GH, Sandson NB, Cozza KL. Gastrointestinal medications. *Psychosomatics* 2007;48:79-85.
24. Silverman JA, Thorgeirsson SS. Regulation and function of the multidrug resistance genes in liver. *Prog Liver Dis* 1995;13:101-23.
25. Thummel KE, Wilkinson GR. *In vitro* and *in vivo* drug interactions involving human CYP3A. *Annu Rev Pharmacol Toxicol* 1998;38:389-430.
26. Rushing DA, Raber SR, Rodvold KA, Piscitelli SC, Plank GS, Tewksbury DA. The effects of cyclosporine on the pharmacokinetics of doxorubicin in patients with small cell lung cancer. *Cancer* 1994;74:834-41.
27. Shi Z, Tiwari AK, Shukla S, Robey RW, Singh S, Kim IW, *et al.* Sildenafil reverses ABCB1- and ABCG2-mediated chemotherapeutic drug resistance. *Cancer Res* 2011;71:3029-41.
28. Sudlow G, Birkett DJ, Wade DN. The characterization of two specific drug binding sites on human serum albumin. *Mol Pharmacol* 1975;11:824-32.
29. Kragh-Hansen U, Chuang VT, Otagiri M. Practical aspects of the ligand-binding and enzymatic properties of human serum albumin. *Biol Pharm Bull* 2002;25:695-704.
30. Oliva F, Gallelli L. Ibuprofen pharmacology and its implications for musculoskeletal disorders. *Funct Neurol* 2010;25:20.
31. Pozzi A, Gallelli L. Pain management for dentists: The role of ibuprofen. *Ann Stomatol (Roma)* 2011;2:3-24.
32. Guengerich FP. Characterization of human cytochrome P450 enzymes. *FASEB J* 1992;6:745-8.
33. Nelson DR, Kamataki T, Waxman DJ, Guengerich FP, Estabrook RW, Feyereisen R, *et al.* The P450 superfamily: Update on new sequences, gene mapping, accession numbers, early trivial names of enzymes, and nomenclature. *DNA Cell Biol* 1993;12:1-51.
34. Nebert DW, Nelson DR, Coon MJ, Estabrook RW, Feyereisen R, Fujii-Kuriyama Y, *et al.* The P450 superfamily: Update on new sequences, gene mapping, and recommended nomenclature. *DNA Cell Biol* 1991;10:1-14.
35. Nakamura K, Goto F, Ray WA, McAllister CB, Jacqz E, Wilkinson GR, *et al.* Interethnic differences in genetic polymorphism of debrisoquin and mephenytoin hydroxylation between Japanese and Caucasian populations. *Clin Pharmacol Ther* 1985;38:402-8.
36. Døssing M, Pilsgaard H, Rasmussen B, Poulsen HE. Time course of phenobarbital and cimetidine mediated changes in hepatic drug metabolism. *Eur J Clin Pharmacol* 1983;25:215-22.
37. Murray M. Drug-mediated inactivation of cytochrome P450. *Clin Exp Pharmacol Physiol* 1997;24:465-70.
38. Murray M. P450 enzymes. Inhibition mechanisms, genetic regulation and effects of liver disease. *Clin Pharmacokinet* 1992;23:132-46.
39. Lillibridge JH, Liang BH, Kerr BM, Webber S, Quart B, Shetty BV, *et al.* Characterization of the selectivity and mechanism of human cytochrome P450 inhibition by the human immunodeficiency virus-protease inhibitor nelfinavir mesylate. *Drug Metab Dispos* 1998;26:609-16.
40. Sutton D, Butler AM, Nadin L, Murray M. Role of CYP3A4 in human hepatic diltiazem N-demethylation: Inhibition of CYP3A4 activity by oxidized diltiazem metabolites. *J Pharmacol Exp Ther* 1997;282:294-300.
41. Wagner F, Kalusche D, Trenk D, Jähnchen E, Roskamm H. Drug interaction between propafenone and metoprolol. *Br J Clin Pharmacol* 1987;24:213-20.
42. Gareri P, De Fazio P, Gallelli L, De Fazio S, Davoli A, Seminara G, *et al.* Venlafaxine-propafenone interaction resulting in hallucinations and psychomotor agitation. *Ann Pharmacother* 2008;42:434-8.
43. Markowitz JS, Wells BG, Carson WH. Interactions between antipsychotic and antihypertensive drugs. *Ann Pharmacother* 1995;29:603-9.
44. Preskorn SH, Alderman J, Chung M, Harrison W, Messig M, Harris S. Pharmacokinetics of desipramine coadministered with sertraline or fluoxetine. *J Clin Psychopharmacol* 1994;14:90-8.
45. Zomorodi K, Houston JB. Effect of omeprazole on diazepam disposition in the rat: *In vitro* and *in vivo* studies. *Pharm Res* 1995;12:1642-6.
46. Meyer UA. Interaction of proton pump inhibitors with cytochromes P450: Consequences for drug interactions. *Yale J Biol Med* 1996;69:203-9.
47. Zomorodi K, Houston JB. Diazepam-omeprazole inhibition interaction: An *in vitro* investigation using human liver microsomes. *Br J Clin Pharmacol* 1996;42:157-62.
48. Levy RH. Cytochrome P450 isozymes and antiepileptic drug interactions. *Epilepsia* 1995;36:S8-13.
49. Jones TE, Morris RG, Mathew TH. Diltiazem-cyclosporin pharmacokinetic interaction – Dose-response relationship. *Br J Clin Pharmacol* 1997;44:499-504.
50. Jones TE, Morris RG. Diltiazem does not always increase blood cyclosporin concentration. *Br J Clin Pharmacol* 1996;42:642-4.
51. Campana C, Regazzi MB, Buggia I, Molinaro M. Clinically significant drug interactions with cyclosporin. An update. *Clin Pharmacokinet* 1996;30:141-79.
52. Gilard M, Arnaud B, Cornily JC, Le Gal G, Lacut K, Le Calvez G, *et al.* Influence of omeprazole on the antiplatelet action of clopidogrel associated with aspirin: The randomized, double-blind OCLA (Omeprazole CLopidogrel Aspirin) study. *J Am Coll Cardiol* 2008;51:256-60.
53. Ho PM, Maddox TM, Wang L, Fihn SD, Jesse RL, Peterson ED, *et al.* Risk of adverse outcomes associated with concomitant use of clopidogrel and proton pump inhibitors following acute coronary syndrome. *JAMA* 2009;301:937-44.
54. Gareri P, De Fazio P, Cotroneo A, Lacava R, Gallelli L, De Fazio S, *et al.* Anticholinergic drug-induced delirium in an elderly Alzheimer's dementia patient. *Arch Gerontol Geriatr* 2007;44:199-206.

55. Ohyama K, Nakajima M, Nakamura S, Shimada N, Yamazaki H, Yokoi T. A significant role of human cytochrome P450 2C8 in amiodarone N-deethylation: An approach to predict the contribution with relative activity factor. *Drug Metab Dispos* 2000;28:1303-10.
56. Muirhead GJ, Wulff MB, Fielding A, Kleinermans D, Buss N. Pharmacokinetic interactions between sildenafil and saquinavir/ritonavir. *Br J Clin Pharmacol* 2000;50:99-107.
57. Page RL 2nd, Mueller SW, Levi ME, Lindenfeld J. Pharmacokinetic drug-drug interactions between calcineurin inhibitors and proliferation signal inhibitors with anti-microbial agents: Implications for therapeutic drug monitoring. *J Heart Lung Transplant* 2011;30:124-35.
58. Sansone-Parsons A, Krishna G, Martinho M, Kantesaria B, Gelone S, Mant TG. Effect of oral posaconazole on the pharmacokinetics of cyclosporine and tacrolimus. *Pharmacotherapy* 2007;27:825-34.
59. Kapil RP, Cipriano A, Michels GH, Perrino P, O'Keefe SA, Shet MS, *et al.* Effect of ketoconazole on the pharmacokinetic profile of buprenorphine following administration of a once-weekly buprenorphine transdermal system. *Clin Drug Investig* 2012;32:583-92.
60. Periti P, Mazzei T, Mini E, Novelli A. Pharmacokinetic drug interactions of macrolides. *Clin Pharmacokinet* 1992;23:106-31.
61. Gallelli L, Giofrè V, Vero G, Gallelli A, Rocca F, Naty S, *et al.* Clarithromycin in the Treatment of Legionella pneumophila Pneumonia Associated with Multiorgan Failure in a Previously Healthy Patient. *Clin Drug Investig* 2005;25:485-90.
62. Somogyi A, Gugler R. Drug interactions with cimetidine. *Clin Pharmacokinet* 1982;7:23-41.
63. Somogyi A, Muirhead M. Pharmacokinetic interactions of cimetidine 1987. *Clin Pharmacokinet* 1987;12:321-66.
64. Garraffo R, Lavrut T, Ferrando S, Durant J, Rouyre N, MacGregor TR, *et al.* Effect of tipranavir/ritonavir combination on the pharmacokinetics of tadalafil in healthy volunteers. *J Clin Pharmacol* 2011;51:1071-8.
65. Gruer PJ, Vega JM, Mercuri MF, Dobrinska MR, Tobert JA. Concomitant use of cytochrome P450 3A4 inhibitors and simvastatin. *Am J Cardiol* 1999;84:811-5.
66. Martin J, Krum H. Cytochrome P450 drug interactions within the HMG-CoA reductase inhibitor class: Are they clinically relevant? *Drug Saf* 2003;26:13-21.
67. Gallelli L, Ferraro M, Spagnuolo V, Rende P, Mauro GF, De Sarro G. Rosuvastatin-induced rhabdomyolysis probably via CYP2C9 saturation. *Drug Metabol Drug Interact* 2009;24:83-7.
68. Venkatesan K. Pharmacokinetic drug interactions with rifampicin. *Clin Pharmacokinet* 1992;22:47-65.
69. Lee KH, Shin JG, Chong WS, Kim S, Lee JS, Jang JJ, *et al.* Time course of the changes in prednisolone pharmacokinetics after co-administration or discontinuation of rifampin. *Eur J Clin Pharmacol* 1993;45:287-9.
70. Burger DM, Meenhorst PL, Koks CH, Beijnen JH. Pharmacokinetic interaction between rifampin and zidovudine. *Antimicrob Agents Chemother* 1993;37:1426-31.
71. Grange JM, Winstanley PA, Davies PD. Clinically significant drug interactions with antituberculosis agents. *Drug Saf* 1994;11:242-51.
72. Koselj M, Bren A, Kandus A, Kovac D. Drug interactions between cyclosporine and rifampicin, erythromycin, and azoles in kidney recipients with opportunistic infections. *Transplant Proc* 1994;26:2823-4.
73. Holtbecker N, Fromm MF, Kroemer HK, Ohnhaus EE, Heidemann H. The nifedipine-rifampin interaction. Evidence for induction of gut wall metabolism. *Drug Metab Dispos* 1996;24:1121-3.
74. Li AP, Reith MK, Rasmussen A, Gorski JC, Hall SD, Xu L, *et al.* Primary human hepatocytes as a tool for the evaluation of structure-activity relationship in cytochrome P450 induction potential of xenobiotics: Evaluation of rifampin, rifapentine and rifabutin. *Chem Biol Interact* 1997;107:17-30.
75. Fromm MF, Busse D, Kroemer HK, Eichelbaum M. Differential induction of prehepatic and hepatic metabolism of verapamil by rifampin. *Hepatology* 1996;24:796-801.
76. Fleishaker JC, Pearson LK, Peters GR. Gender does not affect the degree of induction of tirilazad clearance by phenobarbital. *Eur J Clin Pharmacol* 1996;50:139-45.
77. Rambeck B, Specht U, Wolf P. Pharmacokinetic interactions of the new antiepileptic drugs. *Clin Pharmacokinet* 1996;31:309-24.
78. Backman JT, Olkkola KT, Ojala M, Laaksovirta H, Neuvonen PJ. Concentrations and effects of oral midazolam are greatly reduced in patients treated with carbamazepine or phenytoin. *Epilepsia* 1996;37:253-7.
79. Cropp JS, Bussey HI. A review of enzyme induction of warfarin metabolism with recommendations for patient management. *Pharmacotherapy* 1997;17:917-28.
80. Siniscalchi A, Gallelli L, De Sarro G, Malferrari G, Santangelo E. Antiepileptic drugs for central post-stroke pain management. *Pharmacol Res* 2012;65:171-5.
81. Watkins PB, Wrighton SA, Schuetz EG, Molowa DT, Guzelian PS. Identification of glucocorticoid-inducible cytochromes P-450 in the intestinal mucosa of rats and man. *J Clin Invest* 1987;80:1029-36.
82. Siniscalchi A, Gallelli L, Calabrò G, Tolotta GA, De Sarro G. Phenobarbital/Lamotrigine coadministration-induced blood dyscrasia in a patient with epilepsy. *Ann Pharmacol* 2010;44:2031-4.
83. Carrillo Norte JA. Pharmacokinetic process: Does the site of drug action? Excretion of drugs. *Rev Enferm* 2011;34:24-31.
84. Kido Y, Matsson P, Giacomini KM. Profiling of a prescription drug library for potential renal drug-drug interactions mediated by the organic cation transporter 2. *J Med Chem* 2011;54:4548-58.
85. Kristensen MB. Drug interactions and clinical pharmacokinetics. *Clin Pharmacokinet* 1976;1:22.
86. Ronchera CL, Hernández T, Peris JE, Torres F, Granero L, Jiménez NV, *et al.* Pharmacokinetic interaction between high-dose methotrexate and amoxicillin. *Ther Drug Monit* 1993;15:375-9.
87. Hill G, Cihlar T, Oo C, Ho ES, Prior K, Wiltshire H, *et al.* The anti-influenza drug oseltamivir exhibits low potential to induce pharmacokinetic drug interactions via renal secretion-correlation of *in vivo* and *in vitro* studies. *Drug Metab Dispos* 2002;30:13-9.
88. Wu H, Liu M, Wang S, Feng W, Yao W, Zhao H, *et al.* Pharmacokinetic properties and bioequivalence of two compound formulations of 1500 mg ampicillin (1167 mg)/probenecid (333 mg): A randomized-sequence, single-dose, open-label, two-period crossover study in healthy Chinese male volunteers. *Clin Ther* 2010;32:597-606.
89. Ito S, Kusuhara H, Yokochi M, Toyoshima J, Inoue K, Yuasa H, *et al.* Competitive inhibition of the luminal efflux by multidrug and toxin extrusions, but not basolateral uptake by organic cation transporter 2, is the likely mechanism underlying the pharmacokinetic drug-drug interactions caused by cimetidine in the kidney. *J Pharmacol Exp Ther* 2012;340:393-403.
90. Nies AT, Hofmann U, Resch C, Schaeffeler E, Rius M, Schwab M. Proton pump inhibitors inhibit metformin uptake by organic cation transporters (OCTs). *PLoS One* 2011;6:e22163.
91. Fagerholm U. Prediction of human pharmacokinetics-renal metabolic and excretion clearance. *J Pharm Pharmacol* 2007;59:1463-71.
92. Handler J. Lithium and antihypertensive medication: A potentially dangerous interaction. *J Clin Hypertens (Greenwich)* 2009;11:738-42.

93. Amdisen A. Lithium and drug interactions. *Drugs* 1982;24:133-9.
94. Trifirò G, Corrao S, Alacqua M, Moretti S, Tari M, Caputi AP, *et al.* Interaction risk with proton pump inhibitors in general practice: Significant disagreement between different drug-related information sources. *Br J Clin Pharmacol* 2006;62:582-90.
95. Gallelli L, Galasso O, Urzino A, Saccà S, Falcone D, Palleria C, *et al.* Characteristics and clinical implications of the pharmacokinetic profile of Ibuprofen in patients with knee osteoarthritis. *Clin Drug Investig* 2012;32:827-33.
96. De Fazio S, Gallelli L, De Siena A, De Sarro G, Scordo MG. Role of CYP3A5 in abnormal clearance of methadone. *Ann Pharmacother* 2008;42:893-7.
97. Spina E, Trifiro G. Preventing drug interactions with antidepressants in the elderly. *Aging Health* 2007;3:13.

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