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Clinically important pharmacokinetic drug-drug interactions with antibacterial agents

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ABSTRACT

Antimicrobial agents are widely used, and drug interactions are challenging due to increased risk of adverse effects or reduced efficacy. Among the interactions, the most important are those affecting metabolism, although those involving drug transporters are becoming increasingly known. To make clinical decisions, it is key to know the intensity of the interaction, as well as its duration and time-dependent recovery after discontinuation of the causative agents. It is not only important to be aware of all patient treatments, but also of supplements and natural medications that may also interact. Although they can have serious consequences, most interactions can be adequately managed with a good understanding of them. Especially in patients with polipharmacy it is compulsory to check them with an electronic clinical decision support database. This article aims to conduct a narrative review focusing on the major clinically significant pharmacokinetic drug-drug interactions that can be seen in patients receiving treatment for bacterial infections.

Keywords: Anti-Bacterial Agents, Drug Interactions, Pharmacokinetics, Beta-Lactams, Sulfonamides, Macrolides, Quinolones, Glycopeptides, Rifamycins.

Interacciones farmacocinéticas clínicamente relevantes con agentes antibacterianos

RESUMEN

Los antimicrobianos se utilizan ampliamente y las interacciones farmacológicas representan un desafío debido al aumento del riesgo de efectos adversos o la reducción de la eficacia. Entre las interacciones, las más importantes son aquellas que afectan el metabolismo, aunque aquellas que involucran a los transportadores de fármacos están siendo cada vez más reconocidas. Para tomar decisiones clínicas, es fundamental conocer la intensidad de la interacción, así como su duración y la recuperación dependiente del tiempo después de la discontinuación de los agentes causantes. No solo es importante estar al tanto de todos los tratamientos del paciente, sino también de los suplementos y medicamentos naturales que podrían interactuar. Aunque pueden tener consecuencias graves, la mayoría de las interacciones pueden manejarse adecuadamente con un buen entendimiento de las mismas. Especialmente en pacientes con polifarmacia, es obligatorio verificarlas con una base de datos electrónica de apoyo a la decisión clínica. Este artículo tiene como objetivo realizar una revisión narrativa centrada en las principales interacciones farmacocinéticas farmacofarmacéuticas de importancia clínica que pueden observarse en pacientes que reciben tratamiento para infecciones bacterianas.

Palabras clave: Agentes antibacterianos, interacciones farmacológicas, farmacocinética, betalactámicos, sulfonamidas, macrólidos, quinolonas, glucopéptidos, rifamicinas.

INTRODUCTION

When a patient is hospitalized for an urgent illness, it should be taken into consideration that could probably require medication for other comorbidities, including infections. The possible interaction between these drugs is an important aspect when planning treatment. In patients with polypharmacy, the risk of interactions increases with the addition of new drugs. Studies indicate that between 37-60% of patients may present an interaction during hospital admission, which may cause a loss of efficacy or increased adverse effects [1]. A Turkish multicenter study reported the frequency and potential drug-drug interactions (DDI) in five hospitals. More than 25% of all interactions were associated with antimicrobial agents

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[1]. Not only DDIs are relevant, but also food, vitamins/mineral supplements, and natural products could interact with drugs, increasing adverse effects or otherwise reducing efficacy [2,3].

DDIs usually involve an object drug (victim) and a precipitant drug (perpetrator) that modifies the effect of the object drug. Occasionally a pair of drugs will interact in both directions through one of these two general mechanisms [4].

Pharmacokinetic (PK) interactions occur when the precipitant drug changes the object drug's absorption, distribution, metabolism, or excretion. These interactions are typically managed by monitoring drug concentrations or vital signs [5,6].

Pharmacodynamic (PD) interactions cause changes in the pharmacological response of the drug target organ, without affecting the kinetics of the drug. One drug affects the actions of another drug, causing synergism or antagonism that may involve changes in its efficacy or toxicity, and adjusting doses accordingly [6].

The most important object drugs involved in either PK or PD interactions are those with a low therapeutic index; thus, minor changes in drug concentrations or effects matter more. Also due to patient characteristics, there may be a wide interindividual variability i.e., genetic polymorphisms, renal or hepatic impairment, and even intraindividual variability [2]. Information on DDIs should always be interpreted within the clinical context.

This article aims to conduct a narrative review focusing on the major clinically significant PK DDI that can be seen in patients receiving treatment for bacterial infections. This review will neither deeply cover PD DDI nor PK DDI with other antimicrobials like antiviral, antimalarial, or anti-protozoal drugs.

MATERIAL AND METHODS

Data Sources. A Pubmed search was conducted in July 2023 with the following MeSH terms ("Anti-Bacterial Agents" [Pharmacological Action]) AND "Drug Interactions"[Mesh] that retrieved 19153 results. After limiting article type to clinical trial or meta-analysis or randomized controlled trial or review or systematic review, publication date last 5 years, species: humans and language: English, French or Spanish, 191 results remained, that were manually examined to the final selection of 80 articles. We also reviewed the book by Pai MP, et al. Drug Interactions in Infectious Diseases, nice reviews previously performed, as well as UpToDate and product package inserts/summary of product characteristics (SPC) of new antimicrobials [4,6–8].

Selection Criteria for the Major Interactions. After a review of the literature on PK DDI with the major antibiotic families, the drugs most associated with these interactions were determined. Being a very broad topic, the review was limited to commonly used drugs.

PK DDIs were graded according to UpToDate database as major (classified as "X" -avoid combination- or "D" -consider treatment modification-); moderate (C –monitor therapy) or minor (B –no action needed-) according to clinical significance. In some cases, the summary of product characteristics of the drug was also consulted.

Drugs in each antibacterial were organized by numbers in different sections, while interactive drugs appeared in order of relevance.

KEY CONTENT AND FINDINGS

Each of the four basic processes that determine the PK behavior of a drug- absorption, distribution, metabolism, and excretion- may be affected by other drugs. In the past, major focus was on distribution, particularly plasma protein binding, but nowadays it has been proved that the main cause of DDI is the modulation of the activity (inhibition or induction) of enzymes and transporters. The mechanisms involved in the most important PK interactions are described below.

Pharmacokinetic drug-drug interactions mechanisms

1. Absorption

Gastric pH may change the solubility or the chemical stability of some oral antimicrobials, notably certain azole antifungals (i.e., posaconazole, itraconazole, ketoconazole) and beta-lactam antibiotics (i.e., cefuroxime). The oral bioavailability of these drugs may be modified by proton pump inhibitors or H2-receptor antagonist therapy [4]. Cationic antacids (especially magnesium or aluminum but also, to a lesser degree, calcium, and iron), sucralfate (sucrose aluminum sulfonate), or perhaps kaolin-pectin form insoluble chelates with certain antibiotics including tetracyclines, fluoroquinolones, and maybe lincosamides, reducing the absorption of the antibiotic. Regarding coadministration with meals, some antimicrobial drugs may be taken with or without meals (i.e., acyclovir, azithromycin, amantadine, ciprofloxacin, famciclovir, fluconazole, flucytosine, isavuconazole, levofloxacin, linezolid –avoid foods rich in tyramine and caffeine-, moxifloxacin, oseltamivir, posaconazole tablets, rifabutin, pyrazinamide, valacyclovir). Levofloxacin and moxifloxacin can be taken with milk while administration of ciprofloxacin with milk should be avoided. Conversely, other drugs must be taken with an empty stomach –1 hour before or 1 hour after meals- (i.e., isoniazid, , rifampin). Lastly, sometimes it is preferred to take them with food to improve absorption (i.e., atovaquone, ribavirin, rifapentine, valganciclovir) or for gastrointestinal tolerability reasons (i.e., amoxicillin-clavulanate, cephalosporins, clarithromycin, clindamycin, doxycycline, trimethoprim-sulfamethoxazole, ethambutol, famciclovir, metronidazole -avoid ethanol-) [4,9].

2. Metabolism

Metabolism is a biotransformation process, where endogenous and exogenous compounds are converted to more polar products to ease their elimination from the body. The process of metabolism is divided into 3 phases. Phase I metabolism involves functionalization reactions. Phase II drug metabolism is a conjugation reaction. Phase III refers to transporter-mediat-

Table 1 **Weak, moderate or strong inhibitors or inducers of the main enzymes of Cytochrome P-450. Main substrates of the affected enzymes (adapted from to UpToDate). [42,140]**

CYP 1A2			
Strong inhibitors None	**Strong inducers** None	**Main substrates**	
Moderate inhibitors Ciprofloxacin	**Moderate inducers** None	Agomelatine, Alosetron, Caffeine, Clomipramine, Clozapine, Duloxetine, Melatonin, Olanzapine	Pirfenidone, Propranolol, Rasagiline, Ropinirole, Ropivacaine, Theophylline, Tizanidine
Weak inhibitors Acyclovir, Glecaprevir & pibrentasvir, Valacyclovir	**Weak inducers** Rifampin		
CYP 2B6			
Strong inhibitors None	**Strong inducers** None	**Main substrates**	
Moderate inhibitors None	**Moderate inducers** Efavirenz , Nevirapine, Rifampin (rifampicin) , Ritonavir	Bupropion , Cyclophosphamide , Efavirenz , Ifosfamide , Methadone	
Weak inhibitors None	**Weak inducers** Isavuconazole		
CYP 2C8			
Strong inhibitors None	**Strong inducers** Rifampin (rifampicin)	**Main substrates**	
Moderate inhibitors Sulfamethoxazole & trimetoprim	**Moderate inducers** None	Apalutamide, Dabrafenib, Enzalutamide, Ozanimod, Paclitaxel, Pioglitazone	Repaglinide, Rosiglitazone, Selexipag, Tucatinib, Velpatasvir
Weak inhibitors Favipiravir, Tecovirimat, Trimetoprim	**Weak inducers** None		
CYP 2C9			
Strong inhibitors None	**Strong inducers** None	**Main substrates**	
Moderate inhibitors Fluconazole, Sulfamethoxazole & trimetoprim	**Moderate inducers** Rifampin (rifampicin)	Acenocumarol, Celecoxib, Diclofenac, Etravirine, Flurbiprofen, Fluvastatin, Glyburide, (glibenclamide), Gliclazide, Glimepiride	Lesinurad, Losartan, (active metabolite), Meloxicam, Nateglinide, Phenytoin, Siponimod, Sulfamethoxazol, & trimetoprim, Tolbutamide, Warfarin
Weak inhibitors Voriconazole	Weakinducers Rifabutin		
CYP 2C19			
Strong inhibitors Fluconazole	**Strong inducers** Rifampin (rifampicin)	**Main substrates**	
Moderateinhibitors Voriconazole	Moderateinducers None	Carisoprodol, Cilostazol, Citalopram, Clobazam, Clopidogrel (prodrug), Diazepam, Escitalopram, Esomeprazole	Etravirine, Fosphenytoin, Lansoprazole, Methadone, Omeprazole, Pantoprazol, Phenytoin, Voriconazole
Weakinhibitors Etravirine, Tecovirimat	**Weak inducers** Efavirenz		
CYP 2D6			
Strong inhibitors Quinidine	**Inducers** None	**Main substrates**	
Moderate inhibitors Darunavir , Terbinafine (systemic)		Amitriptyline, Aripiprazole, Atomoxetine, Carvedilol, Clomipramine, Codeine (prodrug), Desipramine, Dextromethorphan, Duloxetine, Eliglustat, Flecainide, Haloperidol, Imipramine, Lisdexanfetamine, Metoclopramide, Metoprolol, Mexiletine	Nebivolol, Nortriptilyne, Paroxetine, Perphenazine, Pimozide, Propafenone, Propranolol, Risperidone, Rucaparib, Sertindole, Tamoxifen (prodrug), Tamsulosine, Tetrabenazine, Tramadol (prodrug), Vortioxetine, Zuclopenthixol
Weak inhibitors Chloroquine , Cobicistat			

Table 1 **Weak, moderate or strong inhibitors or inducers of the main enzymes of Cytochrome P-450. Main substrates of the affected enzymes (adapted from to UpToDate). [42,140] (cont.)**

CYP 2E1			
Strong inhibitors None	**Strong inducers** None	**Main substrates**	
Moderate inhibitors Isoniazid	**Moderate inducers** None	Acetaminophen, Chlorzoxazone	
Weak inhibitors	**Weak inducers** Isoniazid		
CYP 3A4			
Strong inhibitors Atazanavir (boosted*), Clarithromycin, Cobicistat, Darunavir (boosted*), Elvitegravir &tcobicistat, Fosamprenavir &tritonavir, Itraconazole, Ketoconazole, Levoketoconazole, Lopinavir, &ritonavir, Nirmatrelvir &tritonavir, Posaconazole, Ritonavir, Tipranavir &tritonavir, Voriconazole	**Strong inducers** Rifampin (rifampicin)	**Main substrates**	
Moderate inhibitors Clofazimine, Erythromycin, Fluconazole, Fosamprenavir, Isavuconazole, (isavuconazonium sulfate) , Lefamulin, Letermovir	**Moderate inducers** Efavirenz, Etravirine, Nafcillin, Rifabutin, Rifapentine	Abemacxiclib, Alfentanil, Alfuzosin, Alprazolam, Amiodarone, Amlodipine, Apixaban, Aprepitant, Artemeter, &lumefantrine, Atorvastatin, Avanafil, Bedaquiline, Bosutinib, Budesonide, Buspirone, Carbamazepine, Ciclesonide, Cilostazol, Clarithromycin, Clindamycin, Clozapine, Cobicistat, Cobimetinib, Colchicine, Conivaptan, Crizorinib, Cyclosporine, Dabrafenib, Dapsone, Darunavir, Dasatinib, Delamanid, Dihydroergotamine, Disopyramide, Domperidone, Doravirine, Doxorubicin, Dronedarone, Efavirenz, Elbasvir, &tgrazoprevir, Eletriptan, Elvitegravir, Encorafenib, Entrectinib, Eplerenone, Eravacycline, Ergotamine, Erlotinib, Etravirine, Erythromycin, Etravirine, Everolimus, Felodipine, Fentanyl, Fluticasone, Fosamprenavir, Fosaprepitant, Fostematinib, Fostemsavir, Glecaprevir&tpibrentasvir, Hydrocodone, Ibrexafungerp, Ibrutinib, Iinotecan, Isavuconazole, Itraconazole, Ivabradine, Ivacaftor, Ivosidenib	Lapatinib, Lefamulin, Lercanidipine, Lopinavir, Lovastatin, Lumacaftor/ivacaftor, Lurasidone, Macitentan, Maraviroc, Maribavir, Mefloquine, Methadone, Methylergometrine, Midazolam, Midostaurine, Mitotane, Naldemedine, Naloxegol, Neratinib, Nevirapine, Nifedipine, Nilotinib, Nimodipine, Nirmatrelvir, Nisoldipine, Olaparib, Ombitasvir,, paritaprevir, ritonavir, plus dasabuvir, Oxycodone, Palbociclib, Pazopanib, Pimozide, Praziquantel, Pretomanid, Quetiapine, Quinine, Quinidine, Ranolazine, Regorafenib, Ribociclib, Rifabutin, Rilpivirine, Rivaroxaban, Rolapitant, Salmeterol, Sertindole, Sildenafil, Silodosin, Simeprevir, Simvastatin, Sirolimus, Sonidegid, Sorafenib, Sunitinib, Tacrolimus, Temsirolimus, Tezacaftor/Ivacaftor, Ticagrelor, Tofacitinib, Tolterodine, Tolvaptan, Toramifene, Trazodone, Triazolam, Upadacitinib, Vandetanib, Vardenafil, Velpatasvir, Venetoclax, Vincristine, Voriconazole, Zanubrutinib
Weak inhibitors Azithromycin, Ciprofloxacin, Clotrimazole, Elbasvir&tgrazoprevir, Glecaprevir&tpibrentasvirIsoniazid, Quinidine	**Weak inducers** Disopyramide Flucloxacillin Nervirapine		

***Boosted with cobicistat or ritonavir. Inhibitors and inducers of an enzyme (perpetrators of DDI) can alter serum concentrations of drugs that are dependent upon that enzyme for their metabolism (victims of DDI). Clinically significant interactions can occasionally occur due to weak inhibitors and inducers when they are combined with a drug that has a narrow therapeutic index and is highly dependent on that enzyme for its metabolism. Accordingly, specific interactions should be checked in the Package insert or using a drug interaction database.**

ed elimination of drug and/or metabolites from body normally via liver, gut, kidney, or lung [10,11].

The most common phase I drug-metabolizing enzymes are represented by CYP450 (CYP) superfamily. CYP enzymes are distributed throughout various tissues and organs, of which the liver and small intestine are the major contributors to the overall metabolism and elimination of drugs. The alteration of CYP activities can occur by three main mechanisms: reversible inhibition, mechanism-based inactivation (including quasi-irreversible and irreversible inhibition), and induction. Table 1 presents antimicrobials that act as weak, moderate or strong inhibitors or inducers of the main enzymes of CYP and main substrates of the affected enzymes. Genetic polymorphisms and epigenetic changes in CYP genes may be responsible for

inter-individual and interethnic variations in disease susceptibility and the therapeutic efficacy of drugs [10]. The result of a PK DDI may vary if the victim is a prodrug activated through an enzyme that is inhibited by another drug, so the inhibitor may decrease its efficacy. Similarly, an inducer may increase the toxicity of the drug. If the drug has toxic metabolites, an inducer of that metabolic pathway may increase its toxicity.

CYP enzymes can be transcriptionally activated by various xenobiotics and endogenous substrates through receptor-dependent mechanisms leading to enzyme induction. Reversible inhibition refers to competition of two drugs for a CYP. Mechanism-based inhibition of a CYP involves the inactivation of the enzyme through the formation of metabolic intermediates that bind tightly and irreversibly to the enzyme. Therefore, metabolic DDI that arise through mechanism-based inactivation of CYPs can be more severe and long lasting than reversible inhibition. Among antimicrobials, clinically important mechanism based CYP3A4 inhibitors include macrolide antibiotics (i.e., clarithromycin and erythromycin), and anti-HIV agents (i.e., ritonavir and cobicistat) [12].

When we are faced with a DDI, one of the important points to be considered is time-dependent recovery of altered enzyme activity after discontinuation of causative drugs. The time to wait must be sufficient to avoid the carry-over effect of the preceding treatment. Imai H et al. reviewed studies conducted in humans about this topic [13]. In the case of competitive inhibition, time-dependent changes of metabolic capacity are thought to depend on time to elimination (half-life) of the inhibitors themselves. On the other hand, de novo enzyme synthesis is thought to be the rate-controlling factor in mechanism-based enzyme inhibition. The recovery half-lives after mechanism-based inhibition are about 20–50 h. From these data, it is estimated that 90% or more recovery can be achieved 10 days after discontinuation of mechanism-based inhibitors. Regarding enzyme induction, the recovery process is thought to be a composite phenomenon of the residual signaling effects of induction (regulated mainly by nuclear receptors) and enzyme degradation, which is considered the dominant recovery process. The recovery half-lives are approximately 40–60 h after enzyme induction. It is estimated that 90% or more recovery can be achieved 14 days after discontinuation of an inducer. Genetic polymorphisms and CYP families involved could also influence enzyme recovery.

For patients treated concurrently with enzyme inhibitors or inducers and drugs that have a narrow therapeutic range (i.e., a slight reduction in its concentrations causes a loss of efficacy or a small increase causes toxicity, like tacrolimus), careful monitoring is advised during those periods [13].

During phase II drug metabolism, the drugs or metabolites from phase I pathways are enzymatically conjugated with a hydrophilic endogenous compound with the help of transferase enzymes [10]. Glucuronidation is the major phase II drug metabolism pathway and UDP-glucuronosyltransferases (UGTs) the main implicated enzymes [10]. UGT1A1 is the highly expressed phase II enzyme in human, which preferentially metabolizes bilirubin. UGTs are normally highly expressed in the liver and gut. Rifampin is a well-known inducer of the expression of UGTs and decreases exposure of substrates (victim drugs). On the other hand, competition for UGTs may lead to inhibition of metabolism and increased drug exposure.

Transporters (Phase III pathway) are important determinants of drug disposition and response. They are present in many locations, such as liver, kidney, intestine, and brain. Conceptually, uptake transporters help in transferring the molecules into the cells and efflux transporters pump them outside the cell. They are classified into 2 main superfamilies: ATP-binding cassette (ABC) and solute carrier (SLC) transporters. ABC transporters are dependent on the energy (ATP) consumption. Information on substrates, inhibitors and DDI of the main transporters can be found on the website UCSF-FDA TransPortal [14].

3. Renal Excretion

Interference with renal excretion of drugs can cause drug interaction by competition for renal tubular secretion or by altered tubular reabsorption. Renal tubular secretion is generally mediated by a coordinate activity of transporter-mediated uptake across the basolateral membrane of proximal tubular cells by OCT2 and of transporter-mediated export across the luminal membrane by multidrug and toxin extrusion 1 and 2-K (MATE1/MATE2-K). Renal transporter-mediated drug interactions tend to be more modest compared to those mediated by hepatic transporters. Trimethoprim increased metformin AUC by 1.3 to 1.4-fold. Another example is the mandatory use of probenecid to prevent cidofovir nephrotoxicity. Cidofovir renal cytotoxic effects are determined by the uptake transporter organic anion transporter 1 (OAT1) and probenecid is an OAT inhibitor [15].

NARRATIVE REVIEW FINDINGS. MAIN PHARMACOKINETIC DRUG-DRUG INTERACTIONS AFFECTING ANTIBACTERIAL AGENTS

For interactions to be clinically significant, the magnitude of the interaction must be sufficient to affect clinical outcomes, that is, efficacy or toxicity. This is usually the case when the interaction is large in magnitude or the drug victim of the interaction has a narrow therapeutic margin. Several drugs have a pronounced concentration-response relationship and a narrow therapeutic margin. In these cases, drug interactions can cause serious problems, for example, antithrombotic agents, antiarrhythmics, antiepileptics, lithium, and with various antineoplastic and immunosuppressive drugs [16]. Clinically relevant PK interactions are described below.

Information on DDI is often limited, usually from studies in healthy volunteers or clinical cases [17]. Therefore, it is important to report adverse drug reactions (ADR) to the surveillance programs of the respective countries, especially if the toxicity is severe or previously unknown or occurs with newly marketed antimicrobials.

BETA-LACTAM ANTIBIOTICS

Beta-lactam antibiotics are a relatively old group of antimicrobials, which became one of the most widely used due to their broad antimicrobial spectrum and wide therapeutic index. Their introduction from the 1930s onwards completely changed the fight against bacterial infectious diseases [18].

Although these drugs are widely used in daily practice, reports on interactions are scarce and often of minor importance. Most knowledge of interactions with other treatments has been obtained from clinical cases, as there are few prospective studies examining potential interactions. The most often described potential interactions are induction of the CYP3A4 enzyme by flucloxacillin (weak inducer) and/or nafcillin (moderate inducer), effect on intestinal flora, effect on renal clearance (i.e., if the co-administered drug has a higher affinity for the renal transporter, a decrease in tubular excretion of the antibiotic will be seen) and possible decreased plasma protein binding of the drug [6,7,19].

Cefiderocol is a new type of cephalosporin, a catechol-substituted siderophore, similar in structure to cefepime and ceftazidime. In laboratory studies, it has been observed that cefiderocol triggers the activity of CYP3A4. The drug's product information states that it could potentially lower the effectiveness of systemic hormonal contraceptives. Therefore, it's advisable to use an additional contraceptive method while undergoing treatment with cefiderocol and continue this precaution for up to 28 days after the treatment ends. Since cefiderocol's induction of CYP3A4 occurs through a process involving PXR, it might also affect other proteins activated by PXR, such as the CYP2C family and P-gp. However, there's limited information available regarding its practical significance in clinical settings [20].

The major pharmacokinetic interactions of beta-lactams are described as follows:

1. Valproic Acid and Derivatives. (major)

Several retrospective studies of patients receiving valproate proved that plasma levels of this drug decreased when carbapenem antibiotics were added to valproate. Multiple case series conclude that this decrease is significant, greater than 90% [21]. Chai PY et al. conducted a systematic review and meta-analysis until July 2020. The overall increased seizure frequency, expressed as median value and range, amounted to 26.3% (3.85%–100%) during combination treatment although this could also be due in part to the presence of carbapenems (especially imipenem) to which an increased risk of seizures has been attributed. This DDI does not seem to be dose dependent as no difference was found in mean serum valproate concentration between the different doses of valproate or carbapenem during combination treatment. The onset of serum valproate decrease was within one to three days following carbapenem initiation, with the lowest values occurring after 4 to 11 days, and slowly increased to similar pre-carbapenem level within 1 to 2 weeks after carbapenem discontinuation. This interaction was common to all carbapenem antibiotics and could not be reversed by increasing the dose of valproate [21–23].

The specific mechanism responsible for this interaction is not completely understood. Suzuki E et al. investigated it in chimeric mice with humanized livers. Their results strongly support that the interaction is caused by a long-lasting inhibition of hepatic acyl-peptide hydrolase. This enzyme mediates the hydrolysis of valproic acid-glucuronide to regenerate the valproic acid. After co-administration, a more rapid decrease in plasma valproic acid concentration than without carbapenems was seen together with an increase in plasma AUC and urinary excretion of valproic acid-glucuronide. Acyl-peptide hydrolase was strongly inhibited even at 24 h after co-administration of meropenem and valproic acid to the chimeric mice [24].

2. Calcium salts. (major)

As indicated in ceftriaxone SPC, the coadministration of an intravenous infusion of calcium with this antibiotic is contraindicated in neonates less than 28 days old. This contraindication appears as a result of several series of neonatal patients who developed lithiasis due to the presence of calcium precipitates in kidney, lungs or liver. Normally, the liver eliminates a considerable proportion of ceftriaxone in the form of soluble salt. However, ceftriaxone is an anion and, when drug concentrations are high, these anions can bind to calcium ions to form insoluble complexes that precipitate in the biliary system. It appears that stones can form in the same way in the renal collecting system. In a pediatric study, 7.8% of the population was found to have ultrasonographically identified nephrolithiasis, all patients had received normal or high doses of ceftriaxone and had had creatinine, urea and calcium levels unchanged from previous values. In non-neonatal patients, ceftriaxone and calcium-containing intravenous solutions can be administered sequentially of one another if the infusion lines are thoroughly flushed between infusions with a compatible fluid [25,26].

3. Vitamin K Antagonists. (moderate)

When penicillins are concurrently used with vitamin K antagonists, the anticoagulant effect may be potentiated. Monitor for increased INR and for signs of bleeding when initiating a penicillin or cephalosporin, and for INR decrease when discontinuing, including several days after cessation [27].

Although some studies did not detect a change in the INR value in patients treated with warfarin and amoxicillin-clavulanic acid, a large case-control study assessed the increased risk of bleeding in patients chronically treated with vitamin K antagonist who had amoxicillin/clavulanic acid added for infection [28]. The results showed a 3-point increase in the odds ratio for serious bleeding [29].

The possible mechanism of this interaction is not clear but could be related to the eradication of microorganisms in the intestine that produce vitamin K precursors [30]. This depletion of vitamin K stores results in hypoprothrombinemia, even without concomitant treatment with vitamin K antagonists. Although this mechanism is mainly due to PD DDI, alternative

PK mechanisms have been suggested, such as preferential hepatic metabolism of clavulanic acid over warfarin, enhancing the concentrations of the second drug and, consequently, increasing INR. Semisynthetic cephalosporins having a methylthiotetrazole substituent at the 3-position, such as cefoperazone and cefotetan, have been associated with the development of hypoprothrombinemia [29–31]. In contrast, an opposite effect was seen with the concomitant use of warfarin, dicloxacillin, and nafcillin, which resulted in a decreased INR [32].

4. Methotexate. (moderate)

The interaction between cephalosporins, penicillins and methotrexate, leading to an accumulation of methotrexate in the blood, and increased toxicity, has been widely described in several clinical cases of onco-hematologic patients, especially with the simultaneous use of piperacillin-tazobactam [33].

Although the causative mechanisms of this interaction are not clear, some authors propose competition for the organic anion transporter 3 (OAT3). Methotrexate is mainly eliminated by the kidneys through OAT1 and OAT3, whereas most of the penicillins and cephalosporins are also substrates of these carriers (Table 2). Another potential mechanism of interaction is the displacement of methotrexate from serum proteins by cephalosporins (i.e., ceftriaxone), leading to an increase in unbound serum methotrexate, which may result in toxicity [34,35]. Patients receiving penicillins during methotrexate therapy should be closely followed to avoid severe toxicity [35]. Meropenem seems to be a safer alternative in patients treated with high-dose methotrexate [36].

5. Probenecid. (moderate)

Probenecid is a uricosuric and renal tubular blocking agent that inhibits the tubular secretion of penicillin and usually increases penicillin plasma levels by any route the antibiotic is given. A 2-fold to 4-fold elevation has been demonstrated for various penicillins [37]. Some beta-lactams SPC recommend against its use.

Most of the penicillins and cephalosporines, as well as avibactam are substrates of OAT1 and OAT3 transporters that might contribute to its active uptake from the blood compartment and, therefore, affect its excretion. When co-administered with probenecid, studies have shown a decreased renal excretion and increase in AUC of amoxicillin and ampicillin, cefotaxime and meropenem between 50-100%, 80-100%, and 56% respectively [38,39]. Probenecid inhibited avibactam uptake by 56% to 70% in vitro [40].

Clinical relevant DDIs with beta-lactams are summarized in table 3.

MACROLIDES

Macrolide antibiotics are used in the treatment of a variety of infections. Erythromycin is the older macrolide and, by structural modifications, derivates such as azithromycin and clarithromycin have appeared.

Azithromycin and clarithromycin have a broader spectrum of activity including atypical, mycobacterial organisms and selected gram-negative, as well as gram-positive organisms.

Macrolide antibiotics have a variety of PK DDI, which are mostly mediated by the inhibition of hepatic cytochrome CYP3A enzymes. Azithromycin is a weak inhibitor of CYP3A4 while erythromycin is a moderate inhibitor and clarithromycin is a strong inhibitor (Table 1). Even though azithromycin is only a weak CYP3A4 inhibitor is not entirely free of risk due to its inhibition of the P-gp [41]. Clarithromycin and erythromycin are strong inhibitors of P-gp (Table 2).

On the other hand, macrolide antibiotics have a high risk of prolonging the QTc interval. These PD DDI may be reviewed elsewhere [42,43].

The most frequent interactions of macrolide antibiotics are summarized as follows:

1. Statins. (major)

Macrolides inhibits the enzymatic activity of CYP3A4 which plays a role in the metabolism of statins that are CYP3A4 substrates. Co-administration macrolides with statins that are primarily metabolized by CYP3A4, especially simvastatin and lovastatin, may lead to increased serum concentrations of those drugs and increased risk for statin-related adverse reactions, including myopathy and rhabdomyolysis. According to FDA prescribing information, concomitant use of simvastatin / lovastatin and clarithromycin / erythromycin is contraindicated [44,45].

Patel AM et. al evaluated the concomitant administration of clarithromycin or erythromycin with statins, which was associated with a higher risk of adverse events compared with statins alone. [44] Clarithromycin increased the exposition (AUC) of atorvastatin 3.5-fold its original value, and erythromycin increased it by 1.3-fold meanwhile azithromycin had no impact on atorvastatin exposure. Simvastatin is not recommended for co-administration with clarithromycin and erythromycin because of an increase of 11-fold and 4-fold of its AUC, respectively compared with basal values. A similar increase is expected with lovastatin [45–47]. Erythromycin also increased 3-fold the pitavastatin AUC, so the manufacturer recommends not to exceed the dose of 1 mg a day if co-administered [47]. As pitavastatin lacksof appreciable CYP3A4 metabolism, this interaction seems mainly due to transporter mediated PK DDI. Rosuvastatin and fluvastatin are less affected by CYP3A4 inhibition and azithromycin is a weak CYP3A4 inhibitor. These drugs can be considered safer alternatives [46].

2. Immunosuppresants. (major)

Macrolide antibiotics decrease the metabolism of calcineurin inhibitors (CNI) such as cyclosporine and tacrolimus, and mammalian target of rapamycin (mTOR) inhibitors sirolimus and everolimus [48]. Concomitant treatment of clarithromycin and erythromycin with CNI or mTOR inhibitors results in a significant increase of immunosuppressant AUC and Cmax (3-10-fold). A 50% dose reduction is recommended if the

Table 2 **Antimicrobials as substrates, inhibitors, and inducers of the main drug transporters. (Modified from to UpToDate). [41,42,120]**

Inhibitors	Inducers	Substrates	
P-glycoprotein [P-gp] or multidrug resistance protein 1 (MDR1)			
Azithromycin	Rifampin (rifampicin)	Ciprofloxacin (minor)	Lefamulin (major)
Clarithromycin (strong)		Delafloxacin (minor)	Omadacycline (minor)
Erythromycin (strong)		Erythromycin (minor)	Quinidine (minor)
		Fidaxomicin (minor)	Rifampin (rifampicin) (minor)
			Rifaximin (major)
BCRP Breast Cancer Receptor Protein [ABCG2]			
Tedizolid	Rifampin (rifampicin)	Delafloxacin	
OAT1/3 organic anion transporters 1 and 3 [SLC22A6]/[SLC22A8]			
None	None	Amoxicillin	Ciprofloxacin
		Ampicillin	Cloxacillin
		Avibactam	Ertapenem
		Cefaclor	Levofloxacin
		Cefadroxil	Meropenem
		Cephalexin	Norfloxacin
		Cefazolin	Penicillin G; Penicillin V
		Cefditoren	Piperacillin
		Cefixime	
		Cefotaxime	
		Cefoxitin	
		Ceftibuten	
		Ceftobiprole	
		Cefuroxime	
OATP1A2 organic anion-transporting polypeptides (SLCO1A2)			
Rifaximin	None	Levofloxacin	
		Rifaximin	
OATP1B1 organic anion-transporting polypeptides (SLCO1B1)			
Clarithromycin	Rifampin (rifampicin)	Rifampin (rifampicin)	
Fusidic acid		Rifaximin	
Rifampin (rifampicin) single dose			
OATP1B3 organic anion-transporting polypeptides (SLCO1B3)			
Clarithromycin	Rifampin (rifampicin)	Rifaximin	
Fusidic acid		Rifampin (rifampicin)	
Rifampin (rifampicin) single dose			
OCT1 - organic cation transporter 1 (SLC22A1)			
Trimethoprim	None	Ethambutol	
OCT2 - organic cation transporter 2 [SLC22A2]			
Trimethoprim	None	Ethambutol	

Table 3 Summary of clinical relevants DDIs with beta-lactams.

Interaction drug	Clinical relevance	Interaction mechanism	PK Alteration	Ref
Valproic acid	Major	Significant decrease, greater than 90% of valproate serum concentration, probably caused by a long-lasting inhibition of hepatic acyl-peptide hydrolase	Valproate serum concentration	[22,24]
Calcium salts	Major	Coadministration of an intravenous infusion of calcium with ceftriaxone is contraindicated in neonates less than 28 days old, due to the presence of calcium precipitates in kidney, lungs or liver.		[25]
Warfarin	Moderate	When penicillins are concurrently used with vitamin K antagonists, the anticoagulant effect may be potentiated. It could be related to the eradication of microorganisms in the intestine that produce vitamin K precursors. With dicloxacillin, and nafcilliun the opposite effect may occur.		[29]
Methotrexate	Moderate	Cephalosporins and penicillins (especially piperacillin/tazobactam) reduce the elimination of methotrexate by competition for the organic anion transporter 3 (OAT3). Meropenem seems to be a safe alternative.	MTX Cl MTX serum concentration	[33,34]
Probenecid	Moderate	Inhibition of the tubular secretion of penicillin and increase of plasma levels. co-administered with probenecid, studies have shown a decreased renal excretion and increase in AUC of amoxicillin and ampicillin, cefotaxime and meropenem.	50-100% AUC	[38,39]

AUC: area under the curve; DDI: drug-drug interaction; MTX: methotrexate; PK: pharmacokinetics.

combination is used, and daily drug concentration monitoring [49]. There are several case reports of toxicity of CNI and mTOR inhibitors due to administration with clarithromycin. As an example, Cheung et al. described supratherapeutic blood concentrations of tacrolimus due to concomitant use with clarithromycin, which was effectively managed by stopping the macrolide administration and reducing tacrolimus dose. It is recommended to monitor blood concentrations [49–51]. Azithromycin is an inhibitor of P-gp. However, the DDIs between CNI or mTOR inhibitors and azithromycin are mild and no a priori dose adjustment of immunosuppressants is necessary [49].

3. Benzodiazepines. (major)

The serum concentration of midazolam and triazolam may increase when combined with clarithromycin/ erythromycin, as well as the risk and severity of adverse effects (Table 4). Intestinal and hepatic CYP3A4 inhibition by clarithromycin significantly reduced the clearance of midazolam in the elderly. Clarithromycin administration led to an increase in the AUC of midazolam by 3.2-fold following intravenous dosing and 8.0-fold following oral dosing. This is due to the intestinal first-pass effect of midazolam [52].

Alprazolam co-administered with clarithromycin may increase benzodiazepine exposure. Gao X et al. reported a case of lethargy, short-term memory loss, and limb weakness in an older patient in treatment with alprazolam and clarithromycin [53]. Alprazolam AUC also increased 61% when co-administered with erythromycin [54].

4. Other drugs. (major)

Table 4 shows the drugs that should be avoided with a potent CYP3A4 inhibitor due to the risk of increased toxicity, especially if the antimicrobial is prescribed for an extended period [42,43].

5. Digoxin. (moderate)

The serum concentration of digoxin can be increased when it is combined with macrolides. The FDA SPC for digoxin and other resources indicate that macrolides may potentiate digoxin toxicity [55]. The inhibition of the P-gp transporter in the intestine is the likely mechanism of this interaction, as digoxin is a P-gp substrate, and the macrolides may inhibit this transporter.

The increase in digoxin concentrations after an oral dose of 400 mg of clarithromycin is approximately 70%. Gomes T et al. published a population-based PK study in which treatment with clarithromycin, erythromycin, and azithromycin was associated with digoxin toxicity in older people. The risk of digoxin toxicity was found to be higher with clarithromycin than with erythromycin or azithromycin [56,57]. Physicians should recognize this interaction when making prescribing decisions and should consider the use of an alternative when appropriate according to the patient's situation.

6. Ketamine. (moderate)

Ketamine is extensively metabolized in the liver by cytochrome CYP 3A4, 2B6, and 2C9 enzymes. Macrolide antibiotics such as clarithromycin and erythromycin may increase ketamine exposure, particularly in its oral form. After oral administration of ketamine, clarithromycin increased the Cmax of ketamine by 3.6-fold and the AUC by 2.6-fold. This effect is reflected in a high incidence of adverse reactions, so monitoring is recommended [58].

Clinical relevant DDIs with macrolides are summarized in table 5.

Table 4 **Drugs that should be avoided with strong CP3A4/P-gp inhibitors (this list is not exhaustive) [42,43].**

Drugs that are sensitive substrates of CYP3A4 and/or P-gp.	
Abemaciclib	Lurasidone
Alfuzosin	Methylergometrine
Amiodarone	Midazolam (oral)
Aliskiren	Midostaurin
Apixaban	Mitotane
Avanafil	Mometasone*
Bosutinib	Naloxegol
Budesonide (inhaled) *	Nilotinib
Ciclesonide (inhaled) *	Olaparib
Clozapine	Ombitasvir/paritaprevir/ritonavir/dasabuvir
Cobimetinib	Palbociclib
Crizotinib	Pazopanib
Dabrafenib	Pimozide
Colchicine	Quetiapine
Dasatinib	Quinidine
Dihydroergotamine	Ranolazone
Disopyramide	Regorafenib
Domperidone	Ribociclib
Dronedarone	Rivaroxaban
Eletriptan	Salmeterol
Eplerenone	Sertindole
Everolimus	Sildenafil (high dose - pulmonary hypertension)
Fentanyl	Silodosin
Flecainide	Simeprevir
Fluticasone	Simvastatin
Ibrutinib	Sunitinib
Irinotecan	Temsirolimus
Ivabradine	Ticagrelor
Lapatinib	Tolterodine
Lercanidipine	Triamcinolone (systemic)
Lovastatin	Triazolam
Lumacaftor/ivacaftor	

*** Increased systemic exposure and an increased risk of corticosteroid related adverse events. The longer the duration of antimicrobial therapy, the greater the risk (probably minimal risk with 5-7 days). In most cases the toxicity occurred after 3 months or more, even years. Nevertheless, there are also some cases after a brief time (2-3 weeks) with fluticasone and boosted protease inhibitors which are strong inhibitors of CYP3A4. It is recommended if it is possible to use beclomethasone [141,142].**

FLUOROQUINOLONES

Fluoroquinolones are antimicrobial agents used for the treatment of a wide range of bacterial infections [6].

The most often described potential interactions are related to absorption (chelation) or metabolism (ciprofloxacin is a is a moderate inhibitor of CYP1A2; see Table 1). See additional information in the SPC.

1. Divalent or trivalent cations. (moderate-major depending on the drug pair)

Concomitant administration of enteral quinolones with divalent or trivalent cation-containing compounds results in a reduction in quinolones bioavailability. The mechanism that is believed to cause decreased absorption is the formation of insoluble complexes or chelators in the digestive tract [59]. When phosphate-binders are administered concomitantly with a quinolone, reduced absorption occurs due to chelation caused by phosphate binders, demonstrated by a reduction of the Cmax and AUC. This likely results in decreased therapeutic efficacy of quinolone therapy [60].

Studies have found that the absorption of ciprofloxacin is the most affected when it is administered with cations, particularly aluminum, magnesium, or sucralfate, in contrast to levofloxacin which is the quinolone least affected by this interaction. Oral ciprofloxacin-multivalent cation interactions studies found alterations in ciprofloxacin absorption PK parameters when administered simultaneously with aluminum/magnesium (-84 to -91% AUC), sucralfate (-88% AUC), iron (-42 to -67% AUC), calcium (-29 to -42% AUC), zinc (-22% AUC), or multivitamins with minerals [61]. Ciprofloxacin should not be taken with milk or other calcium supplemented foods or beverages [62].

Aluminum, magnesium, and iron reduced the AUC of levofloxacin by 44%, 22%, and 19%, respectively. Moxifloxacin AUC was reduced about 60% by aluminum and magnesium, and 30% by iron. Calcium did not significantly affect levofloxacin or moxifloxacin AUC. Therefore, they can be taken with milk.

The interaction with antacids is higher when they are taken shortly before the quinolone (within 2 h prior) and is probably of not clinical relevance if the antacid is taken more than 2 h apart from the antibiotic [63].

2. Clozapine. (major)

Clozapine is an atypical antipsychotic that is metabolized by the CYP1A2 enzyme; therefore, its elimination may be altered with the concomitant use of ciprofloxacin, an inhibitor of this enzyme. Clozapine may cause myelotoxicity. A study carried out in Finland, adding 250mg of ciprofloxacin every 12h or placebo to clozapine treatment, showed that plasma levels of the antipsychotic increased by up to 29%; they recommended close monitoring of patients treated with both drugs [64]. There are multiple reports describing this interaction as well as possible adverse effects such as increased sedation, rhabdomyolysis in severe cases and even one death attributed to high clozapine concentrations [65]. In contrast, Espnes K et al., published a case report concluding that the interaction was not as pronounced as previously reported, and

Table 5 Summary of clinical relevant DDIs with macrolides

Interaction drug	Clinical relevance	Interaction mechanism	PK Alteration	Ref
Statins	Major	Co-administration macrolides with statins that are primarily metabolized by CYP3A4, especially simvastatin and lovastatin, may lead to increased serum concentrations of those drugs.	AUC 4 – 11 fold	[44]
Immuno-suppressants	Major	Decrease of the metabolism of calcineurin inhibitos and mTOR inhibitors by CYP3A4.	AUC 3 – 10 fold	[49,50]
BZDs	Major	Intestinal and hepatic CYP3A4 inhibition increases serum concentration of midazolam, triazolam and alprazolam.	AUC 3 – 8 fold	[54]
Digoxin	Moderate	Serum concentration of digoxin due to inhibition of the P-gp transporter.	70% digoxin serum concentration	[56]
Ketamine	Moderate	Inhibition of ketamine liver metabolism by CYP3A4. DDI particularly important when ketamine is administered in its oral form.	2.6-fold AUC 3.6-fold Cmax	[58]
Clopidogrel	Moderate	Clopidogrel is administered as a prodrug that needs to be activated by CYP, mainly CYP2C19 and CYP3A4. Erythromycin irreversibly inhibits this activation and may decrease the clopidogrel antiplatelet effect.	ADP-induced platelet aggregation	[143]
Opioid analgesics	Moderate	Some opioid analgesics like fentanyl, alfentanil, hydrocodone, and oxycodone are major substrates of cytochrome CYP3A4. A decrease in cytochrome CYP3A4 activity may impair their metabolism and increase their adverse effects.	AUC 1.3-fold	[144]
Proton Pump Inhibitors	Minor	Clarythromycin inhibits CYP3A metabolism of omeprazole.	AUC 89% of omeprazole	[145]

AUC: area under the curve; ADP: adenosine diphosphate; BZD: benzodiazepines; DDI: drug-drug interaction; PK: pharmacokinetics.

proposing that the increase in concentration suffered by the patient was a consequence of the infection [66].

As advised in SPC, it is recommended to monitor plasma levels when clozapine is used concomitantly with CYP1A2 inhibitors, as increased plasma concentrations and hence a higher frequency of adverse effects may occur. In addition, concomitant use of these two drugs may increase the risk of QT prolongation.

3. Theophylline. (major)

Theophylline is a substrate of CYP1A2. The first case reports of an interaction between quinolones and theophylline were published by Wijanands et al. and Maesen et al., who review the experience of concomitant use of theophylline with ciprofloxacin and the occurrence of adverse effects such as nausea, vomiting, and tachycardia [67,68]. Subsequently, several interaction studies have shown that ciprofloxacin 1000 mg daily, reduced theophylline clearance by 19-32% [67,69]. A case-control study in Ontario evaluated the significance of this interaction and found that the prescription of ciprofloxacin to elderly patients receiving theophylline was common and associated with a nearly two-fold increase in the risk of hospitalization for theophylline toxicity. It is plausible that increased theophylline levels could account for some of the CNS effects originally attributed to ciprofloxacin use [70,71].

The quinolones interact differently with theophylline. A meta-analysis found that ciprofloxacin and norfloxacin had a significant relevance as inhibitors of theophylline metabolism, unlike levofloxacin or moxifloxacin [6].

4. Warfarin/Acenocoumarol. (moderate)

Several studies have found a significant increase in the risk of bleeding in patients treated with warfarin and quinolones, particularly ciprofloxacin and levofloxacin. The probability varied according to time of exposure and type of quinolone. A case-control study of a cohort of elderly people evaluated the risk of bleeding with concomitant warfarin therapy with antibiotics and concluded that there was an increased risk for six antibiotic groups including quinolones [72]. In contrast, many studies of healthy volunteers have reported no change in INR or prothrombin time ratio when quinolones were added to warfarin [73].

The mechanism of this possible interaction has not been elucidated and may involve protein binding, CYP inhibition and alteration of the intestinal flora that contributes to vitamin K synthesis. An important consideration is the impact that infection may play on treatment with vitamin K antagonists. It is currently believed that substances released during inflammation and infection may cause down-regulation of some metabolic enzymes, which could interact with vitamin K antagonists and increase the risk of bleeding. Although the contribution of any of these factors is unknown, this may explain at least part of the discrepancy seen between studies of uninfected subjects and those of individuals receiving fluoroquinolones for an active infection [6].

The concluding recommendation is to monitor for increased INR and/or adverse effects of warfarin when starting quinolone therapy especially in those patients who have been on anticoagulant therapy for a long time. Even most of the studies have been done with warfarin, the same cautions should be applied to acenocoumarol due to similar characteristics [49].

5. Methotrexate. (moderate)

The concurrent administration of methotrexate and ciprofloxacin may cause increased serum concentrations of methotrexate, and therefore increase the risk of toxicity. Methotrexate toxicity can result in anemia, bone marrow suppression, and various types of infections

Several studies have reported that quinolones cause a delay in the elimination of methotrexate generating an increase in toxicity. The mechanism is unclear but is hypothesized to be related to plasma protein binding and a reduction in renal function by competitive inhibition of tubular secretion. One study measured methotrexate concentrations in patients treated with ciprofloxacin and found a delay in elimination and an increase in free methotrexate because of the competitiveness of the two drugs for binding to plasma proteins, a phenomenon already observed between methotrexate and salicylic acid [74]. Another study found that organic anion transporting polypeptides OATP1B1, OATP1B3, and OATP1A2 are involved in methotrexate transport and the last transporter also has the function of carrying levofloxacin. The exact mechanism of this interaction is unknown but may involve competitive inhibition of renal tubular secretion [75]. In addition, ciprofloxacin may interact with hepatic aldolase, the enzyme responsible for metabolizing methotrexate in the liver. Because of these potential interactions, some authors conclude that concomitant administration of these two drugs should be avoided while others recommend careful monitoring of methotrexate levels when it is administered concomitantly with ciprofloxacin and other quinolones, including levofloxacin.

6. Probenecid. (moderate)

Probenecid reduces the renal elimination of the fluoroquinolones by inhibiting their tubular secretion via competitive inhibition of renal organic ion transporters. This drug is a blocker of the renal tubular anion secretion pathway (OAT 1 and 3) and is suspected to inhibit renal clearance/excretion when co-administered with quinolones. In healthy volunteers, probenecid increased the AUC of ofloxacin and ciprofloxacin by 16% and 75%, respectively [76–78].

7. Immunosuppressants. (mild)

There are some controversies, with reports in which co-administration of ciprofloxacin and cyclosporine have caused a transient elevation of serum creatinine, while other published case reports conclude that there is no change in exposure or kinetic parameters of cyclosporine when administered concomitantly with ciprofloxacin or moxifloxacin [79]. Levofloxacin reduced the metabolism of cyclosporine increasing Cmax by 23% and AUC by 26%. It is recommended to monitor renal parameters when cyclosporin is administered with levofloxacin at higher doses (500mg every 12h) [80].

Regarding mycophenolate, it seems that quinolone antibiotics interact by killing glucuronidase-producing bacteria in the intestinal tract. Glucuronidases produced by enteric bacteria act on mycophenolic acid (MPA) glucuronide to liberate MPA, which is then available for re-absorption as part of the enterohepatic recirculation process that is suspected to contribute to up to 40% of MPA exposure. A case report describes an approximate 33% reduction in MPA AUC following introduction of intravenous ciprofloxacin to a bone marrow transplant patient receiving intravenous mycophenolate [81].

Some important PD DDI have been described with quinolones such as QTc interval prolongation, hypoglycemia, tendinitis and tendon ruptude, wich are reviewed elsewere [82].

Clinical relevant DDIs with fluoroquinolones are summarized in table 6.

RIFAMYCINS

The rifamycin antibacterial group includes rifampin, rifabutin, and rifapentine. Often, they are used for the treatment of *Mycobacterium tuberculosis*, *M. avium* complex and chronic staphylococcal infections. Rifampin in combination therapy has a significant role in the management of patients with staphylococcal endocarditis. A comparison of rifabutin and rifampin has shown that rifabutin has more activity against the *M. avium* complex and is equally potent against M. tuberculosis. This drug has awakened a considerable interest, as it affects less the hepatic metabolism and so, it has fewer interactions with other medications. Rifapentine has the advantage of presenting a long elimination half-life (14-18h) that allows the use of weekly regimens in patients with latent tuberculosis infection [83].

Rifamycins, especially rifampin, are potent inducers of the P450 enzyme complex. Rifampin is a strong inducer of CYP3A4 and 2C19, a moderate inducer of CYP2B6, 2C8, 2C9, and a weak inducer of CYP1A2. It also induces glucuronidation (UGT1A1, UGT1A9) and some drug transporters like P-gp and BCRP. A single dose of rifampin inhibits OATP1B1/1B3 and leads to a significant increase in statins exposure (i.e., 6,8-fold for atorvastatin and 127% for pravastatin have been observed with a single dose of rifamycin), whereas after multiple doses of rifampin induction phenomenon can overcome this effect and exposure (AUC) to these statines is decreased. The relative inductive potency of rifamycins towards CYP3A is rifampin > rifapentine > rifabutin. [83] CYP3A4 induction by rifapentine approaches that of rifampin (85-100%) when used daily and is more moderate when used once or twice weekly. This interaction may be delayed in onset but may persist beyond the end of treatment [83,84].

Rifamycins are eliminated by intestinal and hepatic metabolism to deacetylated, hydroxylated and formylated

Table 6 Summary of clinical relevant DDIs with fluoroquinolones.

Interaction drug	Clinical relevance	Interaction mechanism	PK Alteration	Ref
Clozapine	Major	Ciprofloxacin inhibits clozapine metabolism of CYP1A2 enzyme; therefore its elimination may be altered.	29% clozapine serum concentration	[64]
Theophylline	Major	Theophylline is a substrate of CYP1A2 which is inhibited by quinolones, increasing adverse effects such as nausea, vomiting and tachycardia.	29% Cl of theophylline	[67,69]
Immuno-suppressants	Moderate	Levofloxacin inhibits metabolism of cyclosporine but the mechanism is still unknown. MPA exposure may be reducted by quinolone reduction of glucuronidase producing bacteria in intestinal tract.	AUC 26%, Cmax 23% of cyclosporine. 33% AUC of MPA	[81]
Warfarin/ Acenocoumarol	Moderate	The mechanism of this possible interaction has not been elucidated and may involve protein binding, CYP inhibition and alteration of the intestinal flora that contributes to vitamin K synthesis.		[72]
Methotrexate	Moderate	Quinolones cause a delay in the elimination of methotrexate. The mechanism is hypothesized to be related to plasma protein binding and a reduction in renal function by competitive inhibition of tubular secretion.	MTX Cl MTX serum concentration	[75]
Probenecid	Moderate	Probenecid reduces the renal elimination of the fluoroquinolones by inhibiting their tubular secretion via competitive inhibition of renal organic ion transporters.	16% AUC oxafloxacin 75% AUC ciprofloxacin	[76,77]
Rifampicin	Minor	Rifampin causes a reduction in the concentration of moxifloxacin most probably because of rifampin-induced glucuronidation or sulphation.	26-32% Cmax 29-31% AUC moxifloxacin	[146]

AUC: area under the curve; Cl: clearance; DDI: drug-drug interaction; MPA: mycophenolate acid; MTX: methotrexate; PK: pharmacokinetics.

derivatives. The drugs and their metabolites are excreted in the bile and eliminated in the faeces. It is important to remember that exept for rifapentine, repeated administration of rifamycins causes an increase in their clearance due to induction of their own intestinal and/or hepatic metabolism. [85] The autoinduction of rifamycins was reported in a study by Strolin Benedetti M, et al. who found that the CYP3A subfamily is induced by either drug causing a decrease in exposure (AUC). The autoinduction of rifampin is characterized by a decrease in AUC and elimination half-life, while rifabutin only shows a decrease in AUC but no change in half-life. Steady-state conditions are generally reached after the sixth daily dose of rifampin 600 mg or rifabutin 300 mg [86].

Unlike rifampin and rifapentine, which are not metabolized by CYP, rifabutin is a mayor substrate of CYP3A4 and a minor substrate of CYP1A2. Consequently, rifabutin has a higher vulnerability to become a victim of interactions compared to the other rifamycins.

Patients receiving any rifamycin should have their medication regimen carefully analysed for DDIs. Baciewitcz AM, et al deeply reviewed rifamycin DDI [87].

Rifaximin is a non-absorbable (oral bioavailability <1%) rifamycin. It displays a small risk of DDI. According to SPC it is a substrate and a mild inducer of CYP3A. [88] In patients with hepatic insufficiency a DDI with narrow therapeutic index drugs metabolised by CYP3A4 cannot be ruled out due to higher plasmatic concentrations of rifaximin. DDI involving drug transporters caused by rifaximin seems to be unlikely.

1. Anticoagulant and antiplatelet agents. (major)

Many anticoagulant and antiplatelet agents are substrates of CYP enzymes and have narrow therapeutic indices, leading to risk of thrombosis when administered with rifamycin, or bleeding when rifamycin is stopped. A recent review of 29 studies concluded that rifampin in combination with warfarin reduced the AUC of the latter by 15-74% [89]. Two to five-fold increases in warfarin dose are needed to maintain efficacy. Acenocoumarol is similarly affected. The reduction in anticoagulant effects is expected within a week of starting rifampin, and may persist for about 2 to 5 weeks after rifampin has been withdrawn. Rifabutin and rifapentine will likely affect vitamin K antagonists in a similar fashion, but to a lesser extent. This interaction is difficult to manage. It is recommended to avoid the combination or closely monitor INR and ensure a good adherence.

Direct anticoagulants are substrates of CYP3A4 and/or P-gp. A reduction of 20-67% in its exposure (AUC) was seen with rifampin. Such combinations should be avoided or used with great caution and surveillance.[90] Rifabutin and rifapentine will likely affect direct anticoagulants in a similar fashion, but to a lesser extent. In contrast to the previous, heparin has low risk of DDI due to its pharmacokinetic characteristics [90].

Referring to antiplatelet agents, aspirin has scarce risk of DDI. Clopidogrel is a prodrug and CYP2C19 (and possibly CYP3A4) enzymes are responsible for the bioactivation to its active metabolite. Strong CYP2C19 inducers like rifampin increase the exposure to the clopidogrel. Therefore, the risk of bleeding may be increased. As a precaution, avoiding this combination when possible is recommended. In a study of 12 healthy volunteers, rifampin (300 mg twice daily for 14 days) coadministered with clopidogrel (600 mg loading dose followed by 75 mg daily for 7 days) increased the clopidogrel active metabolite AUC and maximum serum concentration approximately 4-fold [91]. Prasugrel is also a prodrug but, in contrast to clopidogrel, coadministration of rifampin (600 mg daily) had no significant effect on the pharmacokinetic parameters of the prasugrel active metabolite or its inhibition of platelet aggregation [92].

2. Inmunosuppressants. (major)

As previously described, rifampin is an inducer of a broad spectrum of enzymes and transporters. Decreases in the blood concentrations of immunosuppressants can have serious consequences. Clinical cases of kidney transplant recipients have reported unusually low levels of cyclosporine when they have been treated with rifampin, resulting in acute graft rejection in one of them [93]. PK studies have determined this was due to an induction of CYP3A4, which disappears after discontinuation of rifampin. In addition to this mechanism, it has been reported that P-gp induction may also contribute to the decrease blood levels of the immunomodulator. Some transplant clinical guidelines recommend avoiding whenever possible the simultaneous use of CNI or mTOR inhibitors with rifampin [49]. However, given the strong sterilizing activity of rifampin in tuberculosis, this drug in not entirely contraindicated in solid organ transplant recipients. When rifampin is used, 2 to 5-fold increments in the daily dose of cyclosporine, tacrolimus and mTOR inhibitors are usually necessary to maintain the immunosuppressant in the therapeutic range. Initially, the dose of the immunosuppressive agent should be doubled and then increased accordingly to daily drug level monitoring until a stable dosage is achieved [49,94]. With close monitoring, the rate of rejection does not seem to be superior with rifampin-based regimens [95]. Adequate adherence to treatment is necessary to avoid fluctuations in blood concentrations. Rifabutin is a less potent CYP3A4 inducer and its use instead of rifampin may make easier the coadministration of CNI and mTOR inhibitors; however, the same recommendations for close monitoring made for rifampin still apply to rifabutin.

Mycophenolate mofetil (MMF) and MPA are substrates of glucuronil-transferases (UGT) and drug transporters (OAT1/3, and OATP1B1/1B3). Rifampin (multiple doses) induces UGT and OATP1B1/1B3. It is recommended to utilize an alternate rifamycin if possible [49].

Prednisolone, the active metabolite of prednisone is a substrate of CYP3A4. Rifampin decreased 28% to 66% the AUC of prednisolone [96]. It is recommended to monitor steroid efficacy and to consider dose increase [49].

3. Other antifungals. (major)

Simultaneous use with CYP3A4 inducers may cause a decrease in bioavailability of azole antifungals and, as a result, a loss of effect. The use of ketoconazole, itraconazole, voriconazole or posaconazole concurrently with a strong CYP3A4 inducer (i.e., rifampin) or within 2 weeks is not recommended. If such a combination cannot be avoided, patients should be closely monitored for evidence of decreased clinical response to antifungal therapy.

The interaction between itraconazole and rifamycin has been reported in several studies and clinical cases over time [97]. In 1998, concomitant administration of itraconazole with rifampin was studied in six patients, it was seen that five of them had an undetectable concentration of antifungal in blood and one had an extremely low concentration [98]. In another study of patients with chronic pulmonary aspergillosis, it was noticed that patients taking these two drugs had 98% lower itraconazole concentrations than patients taking only the antifungal drug [99]. In the case of rifabutin, the results are similar. One study found that 28 patients treated with itraconazole and rifabutin had serum levels of the antifungal 81% lower than 65 patients treated with itraconazole alone [100]. Additionally, rifabutin related toxicity may be seen due to increased rifabutin concentrations. There are no studies of rifapentine with itraconazole, but as it is a metabolism inducer like the other two rifamycins, the recommendations would be the same.

Some case reports also describe a decrease in posaconazole concentrations when rifampin was added to therapy with reductions in posaconazole exposure of 60 to 80%, probably due to UGT induction. In a study in healthy subjects rifabutin (300 mg daily for 17 days) decreased posaconazole's AUC by 49%. Conversely, rifabutin's AUC increased by 72%. This combination should be used only is benefits outweigh risks [87].

In another case-report, rifampin 600 mg daily for 30 days decreased voriconazole's Cmax and AUC by 99% [87]. According to the voriconazole SPC, the combination of voriconazole with rifabutin should, if possible be avoided. However, if the combination is strictly needed, the maintenance dose of voriconazole may be increased from 200 mg to 350 mg orally, twice daily (100 mg to 200 mg orally, twice daily in patients less than 40 kg), with careful monitoring of full blood counts and rifabutin adverse reactions [101].

In a pharmacokinetic study of 24 healthy volunteers, rifampin (600mg daily for 35 days) decreased the isavuconazole (400mg day 1, followed by 100mg daily for 13 days) Cmax and AUC 75% and 97%, respectively [102].

The interaction with fluconazole is milder. Case reports have estimated decreases up to 50% in fluconazole AUC with concomitant rifampin [103]. An increase in fluconazole dosage

Table 7 Summary of clinical relevant DDIs with rifamycins

Interaction drug	Clinical relevance	Interaction mechanism	PK Alteration	Ref
DOACs	Major	Increase of DOACs CYP3A4 and/or P-gp elimination.	20-67% AUC of DOACs	[64]
Warfarin and acenocoumarol	Major	Rifampicin induces vitamin K antagonists metabolism by CYP enzimes.	15-74% AUC of warfarin and acenocoumarol	[67,69]
Immuno-suppresants	Major	Rifampicin induces CYP3A4, and P-gp decreasing blood levels of the immunomodulator. Rifampin induces UGT and OATP1B1/1B3 and increases MMF and MPA elimination. Rifampin induces prednisolone CYP3A4 metabolism.	50% AUC of tacrolimus. 47% AUC of cyclosporine 35% AUC of MMF and MPA. 28-66% AUC of prednisolone	[49]
Azole antifungals	Major	Simultaneous use with CYP3A4 inducers may cause a decrease in bioavailability of azole antifungals and, as a result, a loss of effect. The use of ketoconazole, itraconazole, isavuconazole, voriconazole or posaconazole concurrently with a strong CYP3A4 inducer (i.e., rifampin) or within 2 weeks is not recommended.	60-80% AUC of posaconazole. 99% AUC of voriconazole 97% AUC of isavuconazole 50% AUC of fluconazole	[87,101–103]
Hormonal contraceptives	Moderate	Coadministration of estradiol derivatives and rifamycin causes a decrease in the plasma levels of the former due to metabolic induction by rifamycin.	31-42% AUC of etinyl-estradiol	[105]
Midazolam	Moderate	Concomitant use of midazolam with CYP3A4 inducers causes a reduction in the effect of this benzodiazepine due to a decrease in the exposure (AUC).	69% AUC midazolam	[106]
Other drugs that are major substrates of CYP3A4	Moderate-Major	See Table 1.		

AUC: area under the curve; DDI: drug-drug interaction; DOAC: direct oral anticoagulants; MMF: mycophenolate mofetil; MPA: mycophenolate acid; PK: pharmacokinetics.

may be considered. In case of rifabutin use, no dose adjustment is needed but rifabutin adverse reactions should be monitored.

Rifamycin may be used with other antifungals like amphotericin B or echinocandins. The caspofungin SPC recommends using an increased caspofungin dose of 70 mg daily (after 70 mg loading dose) in adults when coadministered with rifampin [104]. 4.4.4. Hormonal contraceptives. (moderate)

Coadministration of estradiol derivatives and rifamycin causes a decrease in the plasma levels of the former due to metabolic induction by rifamycin. Several studies have shown that CYP3A4 inducers can decrease the AUC of estradiol derivatives by 31-42% [105].

The SPC of the estradiol derivatives warns about a loss of efficiency when they are administered concomitantly with CYP3A4 inducers, recommending the use of an extra method of contraception and the continuation of backup contraception during coadministration and for 28 days after discontinuation of the enzyme inducer to ensure the reliability of the contraception [105].

5. Midazolam. (moderate)

Many PK studies have shown that the concomitant use of midazolam with CYP3A4 inducers causes a reduction in the effect of this benzodiazepine due to a decrease in the exposure (AUC). Induction of both hepatic and intestinal CYP3A4 causes a decrease in the bioavailability of this drug, so orally administered midazolam is more affected than parenterally administered forms. A study with concomitant treatment of IV midazolam and rifampin revealed an increase in the clearance of the first drug from 0.44 +/- 0.2 L x kg/h to 0.96 +/- 0.3 L x kg/h causing a reduction in the effect of the drug [106].

Although there is no information on rifapentine, the recommendation would be similar. In the case of rifabutin, a current review proved a relative dose-dependent induction of CYP3A and P-gp, leading to a 69% decrease in the AUC of midazolam [106].

6. Other drugs. (moderate–major, depending on the drug)

It is difficult to describe them all DDI with rifamycins. Other authors deeply reviewed them [87]. Drugs that are major substrates of CYP3A4 and CYP2C19 (Table 1), and drugs with narrow therapeutic index that are substrates of other enzymes also induced by rifamycin antimicrobials, may have their efficacy reduced when these antimicrobials are added to therapy. Due to the large number of DDI with rifamycins it is always recommended to check them.

In the study conducted by Srinivas NR et al., the impact of rifampicin-induced metabolism on oral versus intravenous

Table 8 Summary of clinical relevant DDIs with fusidic acid

Interaction drug	Clinical relevance	Interaction mechanism	PK Alteration	Ref
Statins	Major	This interaction could be driven by the potent inhibition of human OATP1B1/OATP1B3 (involved in hepatic uptake of statins) by FA.	AUC of rosuvastatin, pravastatin, or fluvastatin.	[119]
Warfarin and acenocoumarol	Moderate	Fusidic Acid SPC warns that FA may potentiate the effects of oral anticoagulants, possibly increasing the anticoagulant effects and requiring a reduction in the anticoagulant dose.		[147]
HIV protease inhibitors	Moderate	Co-administration of FA by the systemic route and HIV protease inhibitors, such as ritonavir and saquinavir, may cause an increase in plasma concentrations of both drugs due to possible mutual inhibition of metabolism, which may result in hepatotoxicity.	AUC of FA, ritonavir and saquinavir 2, 1.6 and 3-fold.	[121]

AUC: area under the curve; DDI: drug-drug interaction; FA: fusidic acid; PK: pharmacokinetics.

antineoplastic agents was evaluated. Specifically, it was observed that orally administered antineoplastics such as navitoclax, cabozantinib, cediranib, and idelalisib experienced reduced exposure and increased clearance, not only due to CYP3A4 induction but also due to the induction of Pgp and UGT. Although, intravenously administered drugs like cabazitaxel and romidepsin did not exhibit these effects from rifampicin, as they are not subject to intestinal CYP3A4 and UGT induction, indicating that alterations in their pharmacokinetic profiles are due to other phenomena [107].

Clinical relevant DDIs with rifamycins are summarized in table 7.

ISONIAZID

Isoniazid is an antibiotic used mainly for the treatment and prophylaxis of tuberculosis. It is important to know when using this drug that it is a moderate inhibitor (and weak inducer) of CYP2E1, and a weak inhibitor of CYP3A4, so it can have DDI with drugs metabolized by these enzymes. Some of the drugs with which caution should be exercised are carbamazepine and phenytoin. An increase in the carbamazepine plasma concentration can trigger symptoms of toxicity. Phenytoin toxicity may be greater in patients with reduced metabolism of isoniazid (i.e., those with N-acetyltransferase polymorphisms) [108]. Other drugs that can also be increased by concomitant administration of isoniazid are warfarin, valproate, diazepam or clozapine [7].

A case of severe acetaminophen toxicity was reported in a patient receiving isoniazid.[109] It could be explained by the induction of the CYP2E1 caused by isoniazid, which appears to generate toxic metabolites in the liver. Isoniazid can also act as a monoamine oxidase inhibitor; this interaction may affect some antidepressants and some types of food like wine and some types of cheese. Finally, concomitant treatment of this antitubercular drug with levodopa can cause Parkinson's decompensation. A case report described a deterioration of the patient when he started treatment with rifampin and isoniazid, with an increase of 37% in the AUC and 33% in the Cmax of levodopa. The authors suggested as a possible mechanism an inhibition of the enzyme dopa decarboxylase, probably caused by isoniazid [110].

In tuberculosis therapy, rifampin and isoniazid are often combined. The inducing effect of rifampin on CYP overcomes the inhibitory effect of isoniazid. Therefore, the overall effect of combination therapy is a decrease in drug concentrations of CYP substrates [111].

ETHAMBUTOL AND PYRAZINAMIDE

Ethambutol is used in empirical treatment regimens for *Mycobacterium tuberculosis*. There are few documented interactions, the best known is the one with aluminum hydroxide. Ethambutol should be given 4 hours apart from antacids [112]. Fatty meals reduce the Cmax (22%), and AUC of the drug compared to fasting drug administration. Nevertheless, ethambutol can be taken with or without food [86].

Ethambutol and pyrazinamide have some PD DDI that can be found in their respective SPC.

GLYCOPEPTIDES, LIPOPEPTIDES, AND LIPOGLYCOPEPTIDES

Vancomycin is a glycopeptide antibiotic administered intravenously for treatment of patients with suspected or proven invasive gram-positive infections, including methicillin-resistant *Staphylococcus aureus* (MRSA). There are a small number of reported interactions of vancomycin with other drugs that are mainly PD (nephrotoxicity, ototoxicity, and neuromuscular block) (see SPC). In newborns, vancomycin clearance was reduced by 18% with concomitant ibuprofen use and by 28% with indomethacin by an alteration in the antibiotic disposition [113]. Finally, orally administered vancomycin may bind to anion-exchange resins such as cholestyramine [9].

Daptomycin is a cyclic lipopeptide that is renally excreted and is not hepatically metabolized, so DDI are unlike because daptomycin neither induces nor inhibits CYP isoforms [114].

Oritavancin is a weak inhibitor of CYP2C9 and CYP2C19 and a weak inducer of CYP3A4 and CYP2D6. Caution should be used during co-administration of oritavancin with drugs with a narrow therapeutic window that are predominantly metabolized by one of the affected CYP450 enzymes (i.e., warfarin), as co-administration may increase (i.e., for CYP2C9 substrates) or decrease (i.e., for CYP2D6 substrates) its concentrations. In a study conducted in healthy volunteers, following a single dose of warfarin 25 mg given alone, or administered at the start, 24 or 72 hours after a single 1,200mg dose of oritavancin, the results showed no effect of oritavancin [115].

The DDI potential of dalbavancin is expected to be low. Dalbavancin is not metabolized by CYP enzymes, and it is neither an inhibitor nor an inducer of CYP enzymes. It is not known if dalbavancin is a substrate or inhibitor for hepatic uptake and efflux transporters [116].

AMINOGLYCOSIDES

Aminoglycosides lack important PK DDI but are associated with some clinically relevant PD DDI such as nephrotoxicity, ototoxicity, and neuromuscular blockade which can be consulted in the SPC [117].

CLINDAMYCIN

Clindamycin is a lincosamide antibiotic used for the treatment of anaerobic, streptococcal, and staphylococcal infections. Its major disadvantage is the substantial risk of Clostridium difficile antibiotic-associated diarrhea. Clindamycin is mainly eliminated by the liver and only 5% to 10% is excreted unchanged in the urine. It is a CYP3A4 substrate, this means that inducers of this isoenzyme may decrease the antibiotic concentration, and inhibitors may increase it [118].

FUSIDIC ACID

1. Statins. (major)

Fusidic acid (FA) is a bacteriostatic antibiotic for which *Staphylococcus*, including strains resistant to penicillin, methicillin, or other antibiotics, are especially sensitive. Therefore, it is of interest in the treatment of methicillin-resistant *S. aureus* infections. Cases of rhabdomyolysis, sometimes fatal, have been reported after prescription of FA and a statin. Therefore, this association is contraindicated. Statin therapy should be discontinued for the duration of systemic FA therapy and can be reinstituted seven days after its last dose. Bataillard et al. describe 75 cases of muscle damage related to this DDI reported in the French national pharmacovigilance database (43 cases) and from a literature review (32 cases). The most reported statins were atorvastatin (60%), simvastatin (22.7%), and rosuvastatin (8.0%). Muscle disorders appeared on average 30 days after initiation of FA. Symptoms were muscle weakness (82%), dark urine (71%), and myalgia (61%). Mean creatine kinase level at diagnosis was 43,890 UI/mL, and acute renal injury occurred in more than half of the cases. Outcome was fatal in 22% of cases and 28% kept sequelae at the end of the follow-up (54 days) [119]. This interaction could be driven by the potent inhibition of human OATP1B1/OATP1B3 (involved in hepatic uptake of statins) by FA [120]. This may explain the occurrence of this interaction with statins which are not metabolized by CYP 3A4, such as rosuvastatin, pravastatin, or fluvastatin [119].

2. Warfarin/acenocoumarol. (moderate)

Although specific published data on this interaction are not available, the FA SPC warns that FA may potentiate the effects of oral anticoagulants, possibly increasing the anticoagulant effects and requiring a reduction in the anticoagulant dose.

3. HIV protease inhibitors. (moderate)

Co-administration of FA by the systemic route and HIV protease inhibitors, such as ritonavir and saquinavir, may cause an increase in plasma concentrations of both drugs due to possible mutual inhibition of metabolism, which may result in hepatotoxicity. A case report describes a 32-year-old man who was HIV-positive and being treated with ritonavir, saquinavir, and stavudine who presented with jaundice, nausea, fatigue, arthralgias, and vertigo approximately 1 week after starting FA (500 mg three times/day). The patient's FA was stopped. Serum concentrations of FA, ritonavir and saquinavir were 2, 1.6 and 3-fold higher greater than the upper limit of normal. Symptoms resolved approximately one month after discontinuation of the drugs, and the patient was able to restart antiretroviral treatment [121].

METRONIDAZOLE

1. Warfarin/acenocoumarol. (major)

Metronidazole is an antibiotic derived from nitroimidazoles indicated mainly for anaerobic microorganisms and protozoa. Metronidazole can interact with other drugs due to the ring in its structure that inhibits (weakly) the hepatic metabolism of several pharmacological compounds metabolized by the CYP450 2C9 and/or CYP3A4 isoenzyme [122,123]. Inhibition of these isoenzymes increases the concentration of drugs such as warfarin and other coumarin anticoagulants.

2. Busulfan. (major)

Busulfan toxicity was increased in 14 patients when coadministered with metronidazole as part of myeloablative regimens prior to stem cell transplantation. Trough serum concentrations of busulfan were increased 79% to 87%.

This combination should probably be avoided and, if needed, increased monitoring for busulfan toxicity is recommended [124].

3. Phenytoin. (moderate)

When metronidazole is taken together with phenytoin, the elimination of the antibiotic may be increased because CYP2A6, the isoenzyme responsible for metabolizing metronidazole, is induced, thus requiring a higher dose of metronidazole to achieve the same outcome. Researchers found that concomitant use of phenobarbital and metronidazole reduced the half-life of metronidazole by 33% and increased clearance by 57% [125].

4. Alcoholic beverages. (clinical relevance is uncertain)

Alcoholic beverages should be avoided while taking metronidazole and for at least one day after, due to the patient potentially experiencing disulfiram-like effects. There are several case reports describing a disulfiram-like reaction occurring with the concomitant administration of metronidazole and ethanol. In contrast, metronidazole has not been shown to be an effective component in creating alcohol aversion, and there exists some controversy as to whether this interaction is clinically relevant. This interaction is generally attributed to metronidazole inhibiting aldehyde dehydrogenase, causing a build-up of acetaldehyde in the blood which is ultimately responsible for the subsequent disulfiram-like effects. One study, however, failed to demonstrate an increase in the serum concentration of acetaldehyde after co-administration, so the true mechanism of this interaction is unknown [126].

Clinical relevant DDIs with fusidic acid are summarized in table 8.

OXAZOLIDINONES

Linezolid is an oxazolidinone antibiotic with activity against multidrug-resistant Gram-positive organisms, showing lipophilic features, excellent tissue penetration including the central nervous system (CNS), and weak reversible non-selective monoamine oxidase (MAO) inhibitory effects at therapeutic serum concentrations.

Gatti M et al. deeply reviewed the post-marketing reporting of serotonin syndrome (SS) due to DDIs with linezolid. Their analysis suggests that linezolid is more likely to induce SS when co-administered with citalopram, escitalopram, and methadone [127].

Although linezolid is unlikely to have clinically important interactions at the CYP level, a study in healthy volunteers showed that rifampin 600 mg once daily for 8 days decreased linezolid Cmax and AUC by 21% and 32%, respectively [128]. Other authors have described decreased linezolid trough concentrations during rifampin therapy in patients [129,130]. The clinical significance of this interaction is unknown, and this combination is used in clinical practice. It is strongly recommended that linezolid serum concentrations be monitored in patients with rifampin co-administration or rifampin pretreatment, especially in critically ill patients [129].

Tedizolid inhibits BCRP and increased AUC and Cmax of the BCRP substrate rosuvastatin by approximately 70% and 55%, respectively. Other BCRP substrates such as imatinib, lapatinib, methotrexate, pitavastatin, rosuvastatin, sulfasalazine, and topotecan also could interact with tedizolid. If possible, its discontinuation should be considered. Tedizolid is a reversible inhibitor of MAO in vitro; however, unlike linezolid, no interaction is anticipated when comparing the IC50 for MAO-A inhibition and the expected plasma exposures in man [131].

TETRACYCLINES

The most used tetracyclines are tetracycline, minocycline, and doxycycline. While tetracycline is majorly excreted by the kidneys, minocycline and doxycycline are metabolized by the liver.

The principal interactions of tetracycline are reflected in the drug absorption and elimination. Concurrent administration of tetracyclines with products containing divalent cations, such aluminum, calcium, magnesium, iron, or zinc, reduced plasma concentrations of tetracyclines from 30% to 90%. Common products containing multivalent cations include antiacids, laxatives, antidiarrheals, multivitamins, sucralfate, molindone, and quinapril tablets. The mechanism of this interaction is based on reactions of chelation, decreased dissolution and binding to antiacid compounds. It is recommended to separate tetracyclines administration of these products by 2 hours to minimize the impact of this interaction [9].

Tetracyclines can increase the plasma concentration of methotrexate; in one case report, the clearance of high-dose methotrexate was reduced by 65% after starting doxycycline [132]. Increases in lithium and ergotamine toxicity have also been described with tetracyclines [133].

The combination therapy with retinoids (isotretinoin, tretinoin, etretinate, and acitretin) is not recommended because of the additive effects on pseudotumor cerebri. The mechanism of this interaction is unclear, but it may be PD, as a result of each agent ability to increase intracranial pressure [134].

TIGECYCLINE

Tigecycline, a semisynthetic derivative of minocycline, is the first agent from the glycylcycline class of antibiotics. Because tigecycline is not extensively metabolized, drugs that inhibit or induce the activity of these CYP isoforms are unlikely to affect the clearance of tigecycline.

The coadministration of tigecycline and a single dose of warfarin in healthy patients resulted in an increase of 88% in R-warfarin AUC and 38% in Cmax, and 29% of S-Warfarin AUC and 38% in Cmax. This increase of warfarin exposure did not alter INR values, because the greatest increase was in the

less active isomer. Even so, it is recommended monitor patients closely if warfarin is co-administered with tigecycline [135].

TRIMETHOPRIM-SULFAMETHOXAZOLE

Trimethoprim-sulfamethoxazole is a synergistic sulfonamide-containing combination antibiotic, particularly useful by *Pneumocystis jiroveci, Toxoplasma gondii, Stenotrophomonas maltophilia* and community-associated methicillin-resistant *S. aureus.*

Relevant PD DDI are hyperkalemia and bone marrow supression as it is mentioned in the SPC sheet [4].

Sulfamethoxazole is a moderate inhibitor of CYP2C9, the CYP isoenzyme responsible for metabolism of the more potent S-warfarin. This DDI has commonly been associated with the potentiation of anticoagulation induced by warfarin. Sulfonylureas are also affected by the inhibition of these isoenzymes, since glyburide, gliclazide, glimepiride, and glipizide are metabolized by cytochrome P450 2C9. Trimethoprim inhibits 2C8 which is responsible for the metabolism of repaglinide, meglitinide. Several clinical studies report an increase in the plasma concentration of antidiabetics leading to increased pancreatic insulin release and symptomatic hypoglycemia [136–138].

Sulfa drugs may displace methotrexate from plasma protein binding sites resulting in transiently higher levels of unbound methotrexate. Additionally, trimethoprim competes with methotrexate for renal tubular elimination [139].

CONCLUSIONS

To conclude, important DDI with antimicrobial drugs may occur. It is mandatory to review DDIs, especially when antimicrobial therapies with high risk of DDI are used, due to the important consequences that may result from therapy failure in the treatment of an infectious disease, or an increased toxicity. Knowing the mechanism of interactions and their duration once the causative drug has been discontinued can help us in their clinical management.

A limitation of this study is its reliance on a single database PubMed. Although PubMed is a reputable source for medical literature, it may not include certain relevant studies, reviews, or reports that are available in other databases, such as Scopus, Web of Science, or other specialized databases.

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