Review Article

Antibiotics and their Major Drug Interaction Profiles

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ABSTRACT

Antibiotic therapy poses significant drug–drug interaction risks due to the frequent co-prescription of antibiotics with other medications in both hospital and community environments. Interactions between these substances may lead to decreased therapeutic effectiveness, enhanced toxicity, or unforeseen clinical consequences. This review highlights the most clinically important interactions between antibiotics and other drugs, focusing on their underlying mechanisms and clinical implications. The interactions discussed are primarily mediated through mechanisms such as changes in absorption, distribution, metabolism, and excretion, as well as pharmacodynamic mechanisms involving additive or antagonistic effects. Variations in renal clearance and enzyme induction or inhibition can significantly alter plasma drug concentrations and affect drug exposure. Some drug combinations may also elevate the risk of adverse effects such as cardiac toxicity, bleeding complications, nephrotoxicity, and central nervous system disturbances. Understanding these interactions is essential for rational prescribing as they can have a substantial impact on treatment outcomes and patient safety. Monitoring closely, adjusting medication doses as required, and being aware of potential risks are crucial to reducing adverse effects. The review highlights the importance of identifying clinically relevant interactions in routine clinical practice and recommends increased prescribing vigilance in both hospital and community environments.

Keywords: Antibiotics, Drug–drug interactions, Pharmacokinetics, Pharmacodynamics, Enzyme inhibition, Enzyme induction, Toxicity, Patient safety.

INTRODUCTION

Antibiotics

Antibiotics are medicines that are used to treat infections caused by bacteria.[1]

Drug Interaction

The interaction of two drugs occurs when one influences the effect of the other. Interactions between medications may lead to serious adverse effects or reduce the therapeutic efficacy of a medication, thereby making the treatment less effective. The risk of drug interactions rises in patients who are taking multiple medications at the same time, a situation known as polypharmacy. Elderly patients frequently experience polypharmacy due to the fact that they often suffer from multiple diseases and require several medications for treatment. The likelihood of adverse drug interactions increases as the number of medications taken rises.[2]

The following antibiotics and their clinically significant drug–drug interactions are summarized below: -

1. Amoxicillin + Clavulanic Acid (Augmentin)
2. Azithromycin
3. Ceftriaxone
4. Ciprofloxacin
5. Doxycycline

1) Augmentin

Amoxicillin-clavulanate is a widely prescribed antibiotic combination used in both primary care and emergency medicine settings. Clavulanic acid acts as a β-lactamase inhibitor, whereas amoxicillin is a semi-synthetic, acid-stable β-lactam antibiotic. Augmentin (amoxicillin/ clavulanate) was developed to treat infections caused by bacteria that produce β-lactamase, enzymes which can inactivate many antibiotics. The combination of amoxicillin with clavulanic acid helps restore activity against resistant bacteria and broadens its antibacterial spectrum.

The medication is commonly used to treat respiratory tract infections, such as community-acquired pneumonia, acute bronchitis flare-ups, sinusitis, and otitis media. The antibiotic is also effective against common pathogens including Streptococcus pneumoniae, Haemophilus influenzae, and Moraxella catarrhalis, which are frequent causes of these infections. It is also used in the treatment of urinary tract infections, skin infections, and soft tissue infections.[3]

Augmentin interacts with following drugs:

1. Warfarin
2. Methotrexate

1) Augmentin and Warfarin –

Warfarin and amoxicillin-clavulanate may interact, potentially leading to higher INR levels and an increased risk of bleeding. Case reports and observational studies have indicated this interaction, but the precise mechanism is still unknown. A suggested mechanism involves blocking the

CYP2C9-mediated breakdown of warfarin, which could lead to higher warfarin levels in the blood and intensify its anticoagulant effect. This mechanism was excluded from the study because no increase in plasma warfarin concentration was observed.

Amoxicillin-clavulanate may also alter the normal intestinal flora responsible for vitamin K production. Decreased vitamin K levels may reduce the synthesis of clotting factors II, VII, IX, and X, thereby increasing the effect of warfarin and raising INR levels. Previous research indicated that broad-spectrum antibiotics can interfere with intestinal bacteria and lead to a vitamin K deficiency. Recent evidence suggests that intestinal bacteria primarily produce vitamin K2 in the colon, where absorption is restricted, implying that the overall impact on vitamin K levels may be negligible. Further research is required to gain a clearer understanding of the relationship between changes in intestinal flora and variations in INR levels associated with warfarin use.[4]

2) Augmentin and Methotrexate:

Amoxicillin–clavulanate may increase methotrexate toxicity by reducing its renal clearance and delaying its elimination from the body. This interaction is thought to occur because penicillin antibiotics competitively inhibit the renal tubular transporters involved in methotrexate excretion, leading to elevated methotrexate concentrations.[5]

2) Azithromycin

Azithromycin (AZM) is a second-generation, broad-spectrum synthetic macrolide antibiotic used in the treatment of a wide variety of bacterial and mycobacterial respiratory and skin infections. The antibacterial activity of this compound is attributed to its capacity to bind to the 50S ribosomal subunit, thereby inhibiting protein synthesis. Azithromycin also exhibits notable antiviral and anti-inflammatory properties, in addition to its antibacterial effects.[6]

Azithromycin interacts with following drugs:

1. Cyclosporine
2. Warfarin

1) Azithromycin and cyclosporine:

Cyclosporine is a widely used immunosuppressive medication in transplant patients. The concurrent administration of azithromycin and cyclosporine has been linked to a clinically significant interaction, especially when azithromycin is given intravenously. Studies have shown that patients receiving stable cyclosporine therapy experienced a significant rise in cyclosporine blood concentrations after starting intravenous azithromycin, with levels eventually returning towards baseline after the antibiotic was stopped. The mechanism of azithromycin's interaction with CYP3A4 is unclear, but may involve altered drug metabolism or P-glycoprotein-mediated transport. Elevated cyclosporine levels may increase the risk of toxicity, including nephrotoxicity and hypertension, making this interaction clinically important and unpredictable. Careful monitoring of therapeutic drugs and appropriate dose adjustment of cyclosporine are recommended when these agents are administered concurrently.[7]

2) Azithromycin and warfarin:

Azithromycin is generally regarded as the preferred macrolide in patients taking Warfarin due to its low potential for cytochrome P450-mediated interactions. Azithromycin does not significantly inhibit CYP3A4, unlike erythromycin and clarithromycin, making a direct pharmacokinetic interaction less likely. Case reports have described INR elevations following concurrent administration, suggesting a potentially clinically relevant interaction in susceptible individuals. The proposed mechanisms include suppression of intestinal flora that is responsible for the production of vitamin K. These reports suggest that an interaction may occur in some patients, even if not all studies have shown a clear interaction. Concurrent therapy with these drugs requires close monitoring of INR.[8]

3) Ceftriaxone

Ceftriaxone sodium, commonly known as ceftriaxone, is a third-generation cephalosporin antibiotic belonging to the aminothiazole-cephalosporin group. It is widely used in the treatment of various community-acquired infections, including those caused by organisms such as Neisseria gonorrhoeae and Salmonella typhi.

Ceftriaxone's long half-life enables once-daily dosing, enhancing convenience in both inpatient and outpatient environments. The drug can be given either through an intravenous or an intramuscular route. Ceftriaxone is often used due to its broad antibacterial activity and its higher resistance to certain beta-lactamase enzymes compared with older antibiotics. Resistance to ceftriaxone has emerged in some bacterial strains, necessitating susceptibility testing prior to its use.[9]

Ceftriaxone interacts with following drugs:

1. Calcium
2. Alcohol

1) Ceftriaxone and Calcium:

Ceftriaxone can interact with calcium present in the blood and form solid particles. Laboratory studies using plasma from adults and newborns demonstrated that increasing calcium concentrations reduce the amount of free ceftriaxone available. This occurs because ceftriaxone binds with calcium to form an insoluble complex or precipitate. The effect was observed at lower calcium concentrations in newborns compared with adults.

The formation of these precipitates can be hazardous, as they may block small blood vessels or accumulate in organs like the lungs and kidneys. This reaction can be particularly serious in newborns and has been associated with severe complications. Ceftriaxone should not be co-administered with calcium-containing solutions, especially in neonates.[10]

2) Ceftriaxone and Alcohol:

Disulfiram-like reactions associated with ceftriaxone and alcohol consumption, particularly in children younger than 18 years, are recognized but extremely rare. This reaction is believed to occur due to inhibition of the enzyme aldehyde dehydrogenase, which normally converts the toxic metabolite acetaldehyde, produced during alcohol metabolism, into acetate. Inhibition of this enzyme results in accumulation of acetaldehyde in the bloodstream, leading to toxic effects.

The severity of the reaction is determined by the level of alcohol consumption and drug exposure. Clinical features of the condition range from mild effects such as flushing and headache to severe reactions, including nausea, vomiting, hypotension, cardiac arrhythmias, and potentially fatal outcomes.[10]

4) Ciprofloxacin

Ciprofloxacin is a second-generation fluoroquinolone antibiotic with a broad spectrum of antibacterial activity, especially against aerobic Gram-negative bacteria including Enterobacteriaceae and Neisseria species. It is widely used due to its effectiveness, favourable safety profile, and extensive global clinical experience, including its use in selected pediatric infections.[11]

Ciprofloxacin interacts with following drugs:

1. Methadone
2. Clozapine

1) Ciprofloxacin and Methadone-

Methadone is primarily metabolized in the liver by cytochrome P450 enzymes, particularly CYP3A4 and CYP1A2. Ciprofloxacin inhibits these enzymes, which may reduce the metabolism of methadone and slow its elimination from the body.

As a result, methadone concentrations may increase and lead to toxicity. The most serious adverse effect is severe respiratory depression, along with symptoms such as excessive sedation and pinpoint pupils. In some cases, serious cardiac arrhythmias, including QT prolongation, may also occur.

This interaction may develop within 24–48 hours after initiation of ciprofloxacin therapy. The risk is greater in patients with liver disease, those receiving other central nervous system depressants, or medications that also inhibit CYP enzymes.

Ciprofloxacin can significantly increase methadone levels by inhibiting its metabolism, potentially causing life-threatening toxicity. Thus, this combination should be used with caution, and patients should be closely monitored for signs of sedation and respiratory depression.[12]

2) Ciprofloxacin and Clozapine

Ciprofloxacin has been associated with a clinically significant increase in serum clozapine concentrations. Clinical observations have shown that concurrent administration of ciprofloxacin may cause a rapid and substantial rise in clozapine levels, with some reports describing up to a five-fold increase within a few days after initiation. This interaction is mainly attributed to inhibition of clozapine metabolism through cytochrome P450 enzymes, particularly CYP1A2 and possibly CYP3A4, leading to reduced drug clearance.

Concurrent infection and other factors can further enhance this interaction by suppressing the activity of hepatic CYP enzymes through cytokine-mediated mechanisms. Previous studies have also reported increases in clozapine plasma concentrations of around 29-80% during co-administration with ciprofloxacin, which supports the presence of a consistent pharmacokinetic interaction. Careful monitoring of plasma concentrations and appropriate dose adjustment are necessary when ciprofloxacin is prescribed with clozapine due to its narrow therapeutic index.[13]

5) Doxycycline

Doxycycline is a broad-spectrum antibiotic and a semi-synthetic derivative of tetracycline with improved oral absorption and a longer duration of action, allowing less frequent dosing.

This antibiotic is effective against a broad spectrum of pathogens including Gram-positive and Gram-negative bacteria, as well as certain parasites that cause malaria. Doxycycline is frequently used to treat a wide range of conditions, including respiratory tract infections, sexually transmitted infections, acne, tick-borne and rickettsial diseases, and to prevent malaria.[14]

Doxycycline interacts with following drugs-

1. Iron supplements
2. Oral contraceptive pills

1) Doxycycline and Iron supplements (ferrous salts)

The absorption of doxycycline is significantly reduced when it is taken at the same time as iron preparations like ferrous sulfate. Doxycycline causes this interaction by forming insoluble iron chelate complexes in the gastrointestinal tract. The complexes have low absorption rates, resulting in decreased systemic bioavailability and reduced therapeutic efficacy. To minimize this interaction, doxycycline should be administered at least 2–3 hours before or after iron supplementation.[14]

2) Doxycycline and Oral contraceptive pills

Combined oral contraceptive pills may be less effective when taken with doxycycline, possibly due to changes in the intestinal bacteria that recycle estrogen. Reducing circulating hormone concentrations can potentially lead to decreased contraceptive efficacy and breakthrough

bleeding. The use of additional barrier contraception is advised during doxycycline therapy and for at least seven days following the completion of treatment.[14]

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REFERENCES

1. Halawa EM, Fadel M, Al-Rabia MW, Behairy A, Nouh NA, Abdo M, et al. Antibiotic action and resistance: updated review of mechanisms, spread, influencing factors, and alternative approaches for combating resistance. Front Pharmacol. 2024;14:1305294. doi:10.3389/fphar.2023.1305294.
2. Cascorbi I. Drug interactions—principles, examples and clinical consequences. Dtsch Arztebl Int. 2012;109(33-34):546-556. doi:10.3238/arztebl.2012.0546.
3. White AR, Kaye C, Poupard J, Pypstra R, Woodnutt G, Wynne B. Augmentin® (amoxicillin/clavulanate) in the treatment of community-acquired respiratory tract infection: a review of the continuing development of an innovative antimicrobial agent. J Antimicrob Chemother. 2004;53(Suppl 1):i3–i20. doi:10.1093/jac/dkh050.
4. Zhang Q, Simoneau G, Verstuyft C, Drouet L, Bal dit Sollier C, Alvarez JC, et al. Amoxicillin/clavulanic acid–warfarin drug interaction: a randomized controlled trial. Br J Clin Pharmacol. 2011;71(2):232-236. doi:10.1111/j.1365-2125.2010.03824.x.
5. Bolhuis MS, Panday PN, Pranger AD, Kosterink JGW, Alffenaar JWC. Pharmacokinetic drug interactions of antimicrobial drugs: a systematic review on oxazolidinones, rifamycines, macrolides, fluoroquinolones, and beta-lactams. Pharmaceutics. 2011;3(4):865-913. doi:10.3390/pharmaceutics3040865.
6. Oliver ME, Hinks TSC. Azithromycin in viral infections. Rev Med Virol. 2021;31(2):e2163. doi:10.1002/rmv.2163.
7. Page RL II, Ruscin JM, Fish D, LaPointe M. Possible interaction between intravenous azithromycin and oral cyclosporine. Pharmacotherapy. 2001;21(11):1436-1443. doi:10.1592/phco.21.17.1436.34431.
8. Shrader SP, Fermo JD, Dzikowski AL. Azithromycin and warfarin interaction. Pharmacotherapy. 2004;24(9):945-949. doi:10.1592/phco.24.9.945.36100.
9. Khan MY, Roy M, Rawal RK, Bansal UK. A review—ceftriaxone for life. Asian J Pharm Res. 2017;7(1):35-48.
10. Bereda G. Ceftriaxone in pediatrics: indication, adverse drug reaction, contraindication and drug interaction. J Addict Ther Res. 2022;6:007-009. doi:10.29328/journal.jatr.1001021.
11. Sharma PC, Jain A, Jain S, Pahwa R, Yar MS. Ciprofloxacin: review on developments in synthetic, analytical, and medicinal aspects. J Enzyme Inhib Med Chem. 2010;25(4):577-589. doi:10.3109/14756360903373508.
12. Samoy L, Shalansky KF. Interaction between methadone and ciprofloxacin. Can J Hosp Pharm. 2010;63(5):382-384. doi:10.4212/cjhp.v63i5.950.
13. Sambhi RS, Puri R, Jones G. Interaction of clozapine and ciprofloxacin: a case report. Eur J Clin Pharmacol. 2007;63(9):895-896. doi:10.1007/s00228-007-0313-5.
14. Holmes NE, Charles PGP. Safety and efficacy review of doxycycline. Clin Med Ther. 2009;1:471-482.