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## Drug interactions with antibiotics

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**Abstract**

When two or more drugs enter simultaneously to the systemic circulation, they interact with each other and may exhibit synergistic, antagonistic or additive effect. Antagonistic effect may reduce the therapeutic index of the drugs. Additive effect may sometimes cause overdose. Synergistic activity may increase the potency. This article is solely dedicated to show some of the drug interactions with antibiotics.

**Keywords:** Drug interactions, synergistic, additive, antagonistic activity

**Introduction**

Your prescription for viral/bacterial fever does not only scribed with antibiotics, but also it is prescribed for the NSAID, anti-emetics etc. Have you ever wondered, whether all these drugs should be given together? Do/Can they have any type of interactions in between them? Or they work separately with different systems? This article is solely dedicated to cover about the Drug interactions in between antibiotics with other drugs.

Drug interactions can be explained in simple terms as “when two drugs are given together, one drug affects the normal pharmacokinetics and pharmacodynamics of the other drug.”

The drug interactions with antibiotics can be additive (interactions with the other drugs results in double of the potency) in action can be synergistic (increase in the drug actions) in nature or can be antagonistic (decrease in drug action) in actions <sup>[1]</sup>.

Overdose may occur if the patient is taking any two drugs and one of the drugs potentiates the function of the other drug. Interactions of the drugs can also increase the side effects of the other drugs. And if the drug inhibits the function of the other drug, then the drug will not be able to exhibit its therapeutic effect. Some of the examples are amoxicillin with clavulenic acid, where clavulenic acid synergizes the action of the amoxicillin by inactivating the resistant causing enzyme beta-lactamase <sup>[2]</sup>.

But if the amoxicillin (bactericidal) is given with sulphonamide (bacteriostatic), the action of amoxicillin is being antagonized by sulphonamides because of its bacteriostatic action (the bactericidal drugs act on the growing bacteria and sulphonamides stop the growth of the bacterial population because of its bacteriostatic action) <sup>[3]</sup>.

**Some important interactions with antibiotics**

**Sulphonamides**

Sulphonamides may increase the effect of oral anticoagulants and methotrexate, probably by displacing these drugs from their binding sites on plasma albumin. Sulphonamides also potentiate the actions of oral sulfonylurea hypoglycemic agents, thiazides and uricosuric agents. In the other hand indomethacin, salicylates and probenecid may displace sulphonamides from their binding site on plasma protein and increase their concentrations in plasma. Drugs that release PABA (e.g. procaine), some members of Vitamin B-complex (e.g. folic acid, nicotinamide) and some amino acids (e.g. glutamic acids, methionine) antagonize action of sulphonamides. Calcium and antacids taken with sulphonamides can decrease oral bioavailability of sulphonamides <sup>[3]</sup>. Use of Bone marrow depressants with sulphonamides results in increased leucopenic or thrombocytopenic effects. Use of cyclosporine with sulphonamides may result in decreased plasma concentrations and potential transplant rejection. Hemolytics and sulphonamide together increases the side effects of the drugs. If the sulphonamide is given with the hepatotoxic medications, then they will increase the hepatotoxicity.

Methamine, in acidic urine breaks down into formaldehyde and forms insoluble precipitate with certain sulphonamide and increase the chance of crystalluria in the urine. Sulphonamide as bacteriostatic drug decreases the action of penicillins which is bactericidal in nature [4].

### Beta-lactam Antibiotics

Combination of beta-lactam antibiotics with aminoglycosides synergizes the activity of aminoglycosides by helping the aminoglycoside to pass through the bacterial cell membrane. [5-10]. Combination of parenteral penicillin with heparin causes coagulopathies [11-17]. The mechanism of coagulopathies may be due to the direct effect of the penicillin on the platelets when combined with heparin it exhibits the additive effect [12, 13, 17]. With the concurrent use of aspirin with penicillin group of antibiotics such as oxacillin, nafcillin, cloxacillin, and dicloxacillin increases the half-life and serum concentrations. Concurrent administration of chloramphenicol (bacteriostatic) with penicillin may antagonize the action of penicillin group of drugs [18, 19]. Concurrent use of cephalosporin group of drugs with antacids decreases the concentrations of antibiotics in blood. Concurrent administration of salicylates, phenylbutazone, and sulphonamides along with penicillins results in displacement of penicillins from their plasma protein binding sites. Penicillin on administration with probenecid or other weak organic acids, is competitively inhibited of tubular secretion and therefore increasing the plasma half life and blood concentrations of penicillin. Acid susceptible penicillins such as penicillin-G should not be administered with normal saline or acidic pH parenteral fluids because they are inactivated by the acidic pH.

### Peptide Antibiotics

#### Polymyxin

Polymyxin group of antibiotics shows synergism with the sulphonamides and trimethoprim against various enterobacteriaceae. Colistin is synergistic in vivo with rifampin or cefidzime against multidrug resistant *P. aeruginosa* (Giamerellos-Bourboulis *et al.*, 2003).

#### Vancomycin

These are the glycoprotein group of drugs which have synergistic action with aminoglycosides against Gram-positive cocci. It appears to be synergistic in vivo with rifampin against staphylococcus aureus. (Gigure *et al.*, 2006)

#### Lincosamides

Combination with spectinomycin appears to give marginally enhanced activity against mycoplasma in vitro. Clindamycin is commonly combined with and aminoglycoside or fluoroquinolone in human medicine to treat or prevent mixed aerobic and anaerobic bacterial infection. Particularly these are associated with intestinal spillage into peritoneum. The combination generally has additive or synergistic effects in vitro against a wide range of bacteria. Clindamycin has synergistic effects with metronidazole against *B. fragilis* but only additive effects with trimethoprim-sulphamethoxazole combination against common gram-negative or gram-positive aerobes. Combination with macrolids or chloramphenicol is antagonistic in vitro. (Gigure *et al.*, 2006)

#### Macrolids

Combination of erythromycin with other macrolids, Lincosamides, chloramphenicol is antagonistic in vitro. Erythromycin has been used alone or with an

aminoglycosides for peritonitis after intestinal spillage, combination of macrolide with fluoroquinolones or aminoglycoside can be synergistic, antagonistic or indifferent, depending on the micro-organism studied (Gigure *et al.*, 2006). Combination of macrolide with rifampin gave synergistic inhibition of *Rhodococcus equi* (Prescott and Nicolson, 1984).

Erythromycin and many other macrolides lead to inactivation of the CYP 450 enzyme complex. Concurrent use of erythromycin increases concentrations of drug that are primarily dependent upon CYP3A metabolism such as theophylline, midazolam, carbamazepine, omeprazole and ranitidine. Clarithromycin and roxithromycin have lower affinity for P450 system than erythromycin and other classic macrolide (except spiramycin) (Gigure *et al.*, 2006).

### Aminoglycosides

Aminoglycosides normally exhibits additive and sometimes synergistic with beta-lactam antibiotics. When the aminoglycosides are combined with beta lactam antibiotics, they show synergistic activity against streptococci, enterococci, pseudomonas and other gram-negative bacteria (Winstanley *et al.*, 1989). Gentamicin exhibits synergistic activity against the gram-positive bacteria like *Rhodococcus equi* and *Listeria monocytogenes*. The reason behind this is mainly beta-lactam antibiotics disrupt the cell wall which makes aminoglycosides to pass into the bacterial cytoplasm and exhibit its action. Aminoglycosides have some physical characteristics like highly polar in nature and therefore they are incompatible with beta-lactam antibiotics when combined in the syringe. Therefore care must be taken to avoid mixing of aminoglycosides with other drugs inside the syringe (Gigure *et al.*, 2006). Combination of lincomycin with spectinomycin enhances the spectinomycin's activity against mycoplasma and *Lawsonia intracellularis*. Loop diuretics and osmotic diuretics aggravate the nephrotoxicity when concurrently administered with aminoglycosides. Risk of respiratory paralysis and neuromuscular blockade increases with concurrent administration of aminoglycosides and neuromuscular blocking drugs. Aminoglycosides and halothane together increase the risk of cardiovascular depression. Cephalosporin and aminoglycosides are contraindicated together because of their nephrotoxicity [3].

### Tetracyclines

Calcium, calcium containing IV fluids (ringer lactate), magnesium, and aluminum containing antacids impairs the absorption of tetracyclines. Iron containing preparations and bismuth subsalicylate also hinder the absorption of the tetracyclines (tetracycline chelates with divalent and trivalent cations which is the phenomenon of chemical antagonism). Tetracycline and tylosin exhibit synergistic activity against *Pasteurella*. In combination with polymyxin, tetracycline exhibits the synergistic activity because polymyxin increases the tetracycline uptake into the bacterial cell wall. (Gigure *et al.*, 2006)

Tetracycline antagonizes the action of beta-lactam antibiotics (bacteriostatic drugs inhibits the growth of bacteria and the bactericidal drugs act only upon growing bacteria). Oral anticoagulants and tetracyclines if administered concurrently, then they may aggravate bleeding by depressing plasma prothrombin activity. Microsomal enzyme inducers like phenytoin and Phenobarbital may decrease the plasma half lives of lipid soluble tetracyclines by increasing their metabolism [3].

### Chloramphenicol

Chloramphenicol should be avoided using concurrently with any bactericidal drugs if the patient has low host defense. Use of penicillin G with chloramphenicol showed to have antagonistic nature in bacterial meningitis and endocarditis in humans. Chloramphenicol act at same bacterial site as the macrolids. Fluoroquinolones also have antagonistic action towards the chloramphenicol. This phenomenon can be explained as since the fluoroquinolones act by disrupting the DNA supercoiling followed by release of autolysins for the cell lysis, the chloramphenicol interferes in this process and inhibits the protein synthesis and therefore the next processes cannot be followed. Since chloramphenicol is a microsomal enzyme inhibitor, it inhibits the oxidation process and the glucouronidation process leading to the slow metabolism and prolongs the pharmacologic activity of concurrently administered drugs. Chloramphenicol therefore increases the duration of action of barbiturate group of drugs. (Gigure *et al.*, 2006)

### Fluoroquinolones

Fluoroquinolones exhibits synergistic activity with beta-lactam, aminoglycosides, vancomycins against some of the bacteria. Ciprofloxacin exhibit antagonistic actions when administered with rifampin and chloramphenicol (Eliopoulos and Moellering, 1996). Fluoroquinolones are seen to exhibit the synergistic actions against strict anaerobes when combined with metronidazole. Fluoroquinolones known to increase the elimination half life of theophylline and caffeine by decreasing the hepatic metabolism (Intorre *et al.*, 1995). Probenecid inhibits the tubular secretion and therefore reduces the renal clearance of ciprofloxacin (Stein, 1988).

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