REVIEW

# Risks of antibiotic treatment

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**Abstract**

**Adverse effects of antibiotics can cause a failure of antibiotic treatment. The authors give a survey of antibiotic toxicity manifestations, according to the target organ systems, with emphasis on identification of at-risk patients and on possible prevention of particular adverse effects. Although antibiotics belong to relatively safe pharmaceuticals, many of them can be a cause of a serious damage to the human organism. Beta-lactam antibiotics are considered the least dangerous. A considerable number of adverse effects, especially the dose-dependent ones, are preventable on condition that the risk factors, as the patient's age, functional capacity of eliminating organs (kidney, liver), associated diseases and simultaneous administration of drugs, are considered. In conclusion, the clinically significant drug interactions of antibiotics are pointed out, being of increasing importance especially in patients with multiple diseases and polypragmatic manner of treatment.** ***(Tab. 2, Ref. 48.)***
**Key words: antibiotics, adverse effects, interactions, toxicity, risk factors, prevention.**

An antibiotic may be qualified as safe on condition that it is effective selectively on microorganisms without influencing the macroorganism. Antibiotics affect the structures or enzyme processes of a bacterial prokaryotic cell, which are absent in a human prokaryotic cell. Although antibiotics are considered relatively safe drugs, they show a frequent occurrence of adverse effects, which is due to frequent prescriptions, as well as to nonrational use (Laurence and Bennett, 1992).

Antibiotic-induced adverse effects may be either of A or of B type.

A type (augmented) adverse effects are dose-dependent. They are associated with pharmacodynamic effect of a drug; they are predictable and preventable. Their incidence is high (more than 1%). Intensity and number of the adverse effects increase proportionately to the drug dose. Incidence of the adverse effects can be decreased by patient's monitoring, considering his pharmacokinetic differences and by dosage individualization.

B-type (bizarre) adverse effects are not dose-dependent. They are regarded as idiosyncratic reactions, and this indicates that the exact mechanism of their development is unknown. They do not depend on pharmacodynamic effect; they are mediated by organism's immune reactions to a particular drug, as well as by genetic divergencies of drug metabolism, which leads to the production of a toxic metabolite. These adverse effects result from different reactions of patients, and consequently they are called "patient's reactions". They appear unexpectedly, it is difficult to foresee them, they are almost unpredictable. They are usually very severe and frequently result in death (Rawlins and Thompson, 1985).

The following text brings a survey of adverse effects affecting particular systems (Tab. 1).

## Hypersensitive reactions

Skin reactions to antibiotics are caused most frequently by beta-lactam antibiotics and sulfonamides, rarely by macrolides and aminoglycosides. The incidence of hypersensitive reactions after penicillins varies from 5 % to 10 %, after cephalosporins 3–5 % (Kriska and Krcmery, 2000). The ocurrence of cross-allergic reactions between penicillins and cephalosporins is estimated to 5–10 % (Rajagopalan and Yoshikawa, 2001). Skin re-

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This work was supported by grant No. 176/2002/UK of Comenius University.

**Tab. 1. Survey of adverse effects according to target systems.**

| Toxicity | Antibiotics | Notes |
|---|---|---|
| hypersensitivity | beta-lactam atb, sulfonamides | skin reactions, anaphylaxis, serum sickness, drug fever |
| haemotoxicity | chloramphenicol, sulfonamides | cytopenic reactions |
| nephrotoxicity | aminoglycosides, glycopeptide atb, cephalosporins of I. generation, sulfonamides, quinolones | increased risk in patients with CHRI, hypovolaemia, and simultaneous administration of several nephrotoxic substances |
| gastrointestinal toxicity | broad-spectrum atb, (lincosamides, tetracyclines of I. generation, ampicillin) | GIT discomfort, diarrhoea, pseudomembranous enterocolitis |
| hepatotoxicity | isoniazid, fluoroquinolones, erythromycin-estolate, sulfonamides | hepatocellular, biliary or combined injury |
| CNS toxicity | imipenem, fluoroquinolones | convulsions, sleepiness, confusion, tremor |
| ototoxicity | aminoglycosides | increased risk in patients with preceding hearing disorders, in simultaneous administration of several ototoxic substances |
| cardiotoxicity | fluoroquinolones, erythromycin | prolongation of QT interval |

atb — antibiotic(s); CHRI — chronic renal insufficiency

actions are clinically manifested as maculopapular exanthema, urticaria, erythema multiforme, or Stevens-Johnson syndrome (Cunha, 2001).

Anaphylactic reactions after antimicrobials appear most frequently after sulfonamides and beta-lactam antibiotics. Monobactam aztreonam is reported to have no cross-allergic reactions with penicillins and therefore it can be administered even if there is a history of anaphylactic reaction to penicillins (Johnson and Cunha, 1995). Administration of any kind of penicillin preparations is contraindicated in patients with history of penicillin hypersensitivity. Hypersensitivity examination by means of the skin test is associated with a risk of severe allergic reaction, so it is not performed routinely.

Serum sickness occurs first of all after beta-lactam antibiotics (high frequency of this adverse effect is reported after cefaclor), sulfonamides, and rarely after fluoroquinolones. It appears usually after 2 weeks following the treatment. Manifestations include a moderate increase in body temperature, arthralgia, myalgia and generalized lymphadenopathy (Ball, 1997, Kelkar and Li, 2001).

Fever as a manifestation of hypersensitivity can be caused especially by penicillins and sulfonamides. Drug etiology of fever is indicated by a history of atopy, relative bradycardia in regard to the degree of fever, good general condition and appearance of a patient, not corresponding to the present febrile state. As soon as the drug is discontinued, fever usually decreases in 48–72 hours (Hanson, 1991; Johnson and Cunha, 1996; Kriska, 2000).

Administration of tetracyclines (rarely doxycycline and minocycline), sulfonamides, trimethoprim and quinolones can induce skin photosensitization (Vassileva et al, 1998).

The "red man syndrome" arises after a quick intravenous injection of vancomycin. The reaction is a result of massive elimination of histamine from skin mastocytes. It is not a true allergic reaction. It can be prevented by a slow application of vancomycin (Wallace et al, 1991).

**Haemotoxic reactions**

Leukopenia and thrombocytopenia belong to the most frequent haematologic adverse effects. The best-known of haemotoxic reactions is aplastic anaemia following the treatment with chloramphenicol. This reaction, belonging to the dose-independent ones of B-type, with incidence of 1:20 000 and mortality of

more than 50 %, has caused a markedly limited use of this antibiotic with broad-spectrum antibacterial effect. The more frequent occurrence of the reaction has been reported in patients with simultaneous liver disease (especially with acute hepatitis). Other type of a dose-dependent reaction is reversible neutropenia.

At present, after cutting down the prescription of chloramphenicol, cytopenia (leukopenia, thrombocytopenia) caused by sulfonamides (cotrimoxazole) has become a much more frequent problem. Reversible dose-dependent neutropenia has been reported in the treatment with methicillin, occurring rarely also with natural broad-spectrum oral penicillins, parenteral cephalosporins, vancomycin and metronidazole.

Anaemia can be induced by several mechanisms. Autoimmune haemolytic anaemia with positive Coombs test can be caused by beta-lactam antibiotics, quinolones, and sometimes by rifampicin (Ball, 1997).

A fluoroquinolone with a broadened spectrum, temafloxacin, was abandoned after the causal nexus between its administration and haemolytic anaemia had been confirmed. It is presumed that an immune-complex mechanism of reaction is involved (Blum et al., 1994).

Predisposing factors to haemolytic anaemia induced by sulfonamides are divergences in haemoglobin structure (sickle-cell anaemia) and erythrocyte metabolism disorders (deficiency of glucose-6-phosphate dehydrogenase). Treatment with cotrimoxazole may be associated with occurrence of megaloblastic anaemia, due to antagonistic effect of cotrimoxazole on folic acid metabolism (Frisch, 1973; Kriska and Krcmery, 2000).

Antipseudomonal penicillins (especially carbenicillin) can deteriorate the aggregability of thrombocytes due to an immune-mediated mechanism (Lang et al, 1991). A cephalosporin drug, moxalactam deteriorates the ADP-induced thrombocyte aggregation.

Cephalosporins with a methyl tetrazole side chain in the molecule (cefamandole, cefotetan, cefoperazone) can lengthen prothrombin time because of interference with synthesis of K-vitamin-dependent coagulation factors. Patients with a decreased hepatic store of reduced glutathione (patients with liver diseases, chronic renal insufficiency, neoplasms, ileus, postoperative states) are predisposed to the above mentioned adverse effect. It can be prevented by K-vitamin substitution (Krcmery et al, 2001; Lipsky, 1988; Manian et al, 1990).

**Nephrotoxic reactions**

Antibiotics can deteriorate toxically the glomerular or tubular part of the nephron. Tubular toxicity is more frequent. The most important pathomechanisms of toxicity are: direct toxicity (aminoglycosides, cephalothin, cephaloridine) and an immune-mediated injury (penicillins, e.g. methicillin) (Ball, 1997).

Aminoglycoside antibiotics possess a high tubulotoxic potential when a several-dose daily regime is used. After intravenous application, they are being cumulated in tubular cells. Consequently, they are eliminated by active transport from tubular cells and a decrease of their toxic intracellular concentration occurs. In more frequent dosage than one dose daily, the tubular cell has not sufficient time for active excretion of an aminoglycoside. The therapeutic effect depends on a top concentration of aminoglycosides reached in serum, urine and kidney tissue. The prolonged postantibiotic effect of aminoglycosides is useful. There is only a little difference in nephrotoxic potential of the individual drugs in the group, except netilmicin that is less toxic. Even glycopeptide antibiotics, carbapenems and cephalosporins of the I generation (cephaloridine, cephazolin, cephalothin) can be nephrotoxic (Krcmery et al, 1996; Mingeot-Leclercq and Tulkens, 1999; Rybak et al, 1999).

Interstitial nephritis based on hypersensitivity may be related to administration of beta-lactam antibiotic and quinolones. Sulfonamides can form insoluble crystals, which leads to haematuria, albuminuria, crystalluria, renal colic and even acute renal insufficiency. Sulfonamide crystallization is supported by acid urine pH and dehydration. Prevention consists in sufficient hydration, drinking of alkaline mineral waters, avoiding the drugs that acidify urine (acetylosalicylic acid) (Lomaestro, 2000; Simon and Stille, 1998).

Nephrotoxic risk of antimicrobials is increased with the age of a patient, preexisting renal diseases, hypovolaemia, hypotension, shock, prolonged treatment, simultaneous administration of several potentially nephrotoxic substances (e.g. aminoglycosides, vancomycin, furosemide, cephalosporins, amphotericin B, nonsteroidal antiinflammatory agents, radiocontrast substances). To prevent nephrotoxicity it is necessary to hydrate the patient sufficiently, to individualize dosage according to creatinine clearance, to monitor aminoglycoside levels, to control regularly the parameters of renal function (serum creatinine, urea, creatinine clearance). An increased level of serum $beta_2$-microglobulin and higher activity of N-acetyl-beta-D-glucosaminidase in urine are considered early markers of renal damage (Goetz and Sayers, 1993; Krcmery, 2000; Mesko and Nosalova, 1998).

**Gastrointestinal adverse effects**

Gastrointestinal discomfort is one of the most frequent adverse effects of antibiotics. Nausea and vomiting are frequent adverse effects of macrolides, tetracyclines and fluoroquinolones (Cunha, 2001).

Broad-spectrum antibiotics can cause the overgrowth of the strains of Clostridium difficile and colonization of a bowel. The toxin of this bacterium is responsible for the development of pseudomembranous enterocolitis. It appears most frequently following the treatment with clindamycin, ampicillin, amoxicillin and cephalosporins, rarely after aminoglycosides, quinolones and metronidazole. Hospitalized newborns and elderly patients with decreased immunity are at-risk individuals. The first-choice drug is oral metronidazole or vancomycin (Greenwood, 1997; Kelly et al, 1994).

Broad-spectrum antibiotics cause frequently diarrhoea, arising in consequence of impaired intestinal biocenosis without Clostridium difficile overgrowth. The large intestine can be col-

onized by overgrowing staphylococci or candidae. Gastrointestinal tolerance is dependent upon antibiotic absorption in a proximal part of the gastrointestinal tract (GIT). Ampicillin causes diarrhoea more frequently than amoxicillin does, owing to its less absorption in the proximal part of the GIT. Consequently high ampicillin concentration in the large intestine liquidates physiological anaerobic microflora and has an irritative effect on the intestinal mucosa. The occurrence of diarrhoea after parenteral antibiotics depends on a degree of their excretion into bile (more frequent occurrence after cefoperazone). Erythromycin is capable of increasing the intestinal motility due to stimulation of motilin receptors (Bergogne-Berezin, 2000).

**Hepatotoxic reactions**

A liver injury may be manifested as elevated transaminases, hepatitis, cholestatic syndrome, or as a combination of the mentioned states. The most severe complication of the treatment with isoniazid is hepatitis with multilobular necrosis. It is due to a metabolit of isoniazid – acetylhydrazine. Chronic active hepatitis induced by isoniazid as well as by nitrofurantoin often develops into liver cirrhosis. Hepatitis also can be caused by betalactam antibiotics, especially by oxacillin. Some fluoroquinolones (grepafloxacin, temafloxacin, trovafloxacin) have been abandoned because of rare but particularly severe, almost fatal reactions (Lucena et al, 2000). Liver damage caused by tetracyclines usually occurs only when they are overdosed.

Cholestatic icterus has been reported after treatment with erythromycin – estolate. A mixed type of hepatocellular and biliary injuries appears after the administration of sulfonamides (Farrell, 1997; George and Crawford, 1996; Lochmann, 1990; Reddy and Schiff, 1995).

At-risk patients, predisposed to hepatotoxicity, are those with previous liver diseases (virus hepatitis, alcoholic liver injuries). In isoniazid treatment hepatotoxic manifestations occur frequently with slow acetylators.

Drinking alcohol during the treatment with cephalosporins that have a methyl tetrazole group in the molecule, can produce an antabuse reaction (Kriska and Krcmery, 2000).

**Neurotoxic reactions**

They belong to relatively infrequent adverse effects of antibiotics. An application of imipenem and fluoroquinolones may be associated sporadically with functional disorders of the central nervous system (CNS) (spasms, epileptic convulsions, sleepiness, dizziness, tremor, confusion). They occur especially in the patients with a previous disease of CNS and with a decreased eliminatory function of the kidney; therefore an inevitable reduction of the dose must be made according to creatinine clearance values. Meropenem unlike imipenem does not lead to any of the adverse effects concerning the CNS and can be used for the treatment of neuroinfections (Drusano and Hutchison, 1995; Hantson et al, 1999; Jaspers et al, 1998; Takayama et al, 1995). Disorders of neuromuscular transmission are reported after intraperitoneal administration of neomycin as well as of other aminoglycosides. The disorders occur frequently in a simultaneous administration of curariform myorelaxants. Peripheral neuropathy is reported in relation with a prolonged treatment with metronidazole and with an antituberculotic – isoniazid.

Aminoglycosides and glycopeptide antibiotics possess an ototoxic potential; they impair cochlear, as well as vestibular structures. Their ototoxicity is graduated by a prolonged treatment with high doses, an older age, preceding hearing disorders and simultaneous taking of other drugs with potential ototoxicity (furosemide and ethacrynic acid). Prevention of ototoxicity includes: monitoring of the serum antibiotic level, individualization of the dosage according to creatinine clearance values, active searching for the symptoms of cochlear (tinnitus) and vestibular (dizziness, ataxia) injuries, audiometry. The ototoxic potential of all aminoglycosides is approximately the same, only netilmicin has a slightly lower ototoxic effect. An isolated injury of cochlear apparatus can be caused by a quick intravenous application of erythromycin. Dizziness can be induced by minocycline cumulation in the cells of vestibular apparatus. This injury is reversible (Laurence and Bennett, 1992; Rajagopalan and Yoshikawa, 2001).

An antituberculotic ethambutol can cause optic neuritis and a subsequent blindness. This reaction is dose-dependent. It appears especially in the patients, whose dose is higher than 25 mg/kg per day (Snavely and Hodges, 1984).

**Cardiotoxic reactions**

Some antibacterial agents can induce arrhythmias by influencing directly the excitable structures of the myocardium. Some antibiotics (erythromycin, several newer fluoroquinolones – sparfloxacin, grepafloxacin) induce a prolongation of QT interval and a patient is jeopardized by possible arising of malignant ventricular arrhythmias of the type torsade de pointes (Lipsky and Baker, 1999; Viskin, 1999).

A case of trovafloxacin-induced hypotension has been reported, where vasopressors and volume expanders must be used to manage successfully the state.

The intravenous application of cephalosporins, erythromycin can produce a local irritation resulting in thrombophlebitis (Ball, 1997).

**Tendinitis and tendon ruptures**

They have been reported after ofloxacin and pefloxacin, occurring more frequently in sportsmen, following overloading (Ribard et al, 1992).

**Antibiotic drug interactions**

Serious drug interactions leading to discontinuing the treatment or even to the patient's death, develop on the level of drug biotransformation in the liver. Most drugs are metabolized by a system of oxidoreductases, whose key enzyme is a cytochrome

**Tab. 2. Clinically significant interactions caused by CYP 450 inhibition (revised according to Micuda et al, 1998; Kriska and Krcmery, 2000).**

| Inhibitor+ | Clinical sequelae |
|---|---|
| antihistaminics (terfenadine) | cardiotoxicity – prolongation of QT interval |
| prokinetics (cisapride) | cardiotoxicity – prolongation of QT interval |
| benzodiazepines (midazolam) | prolonging and intensifying of effect |
| immunosuppressives (cyclosporine) | increase of toxicity |
| anticoagulants (warfarin) | haemorrhagic complications |
| hypolipidemic agents (lovastatin) | increased risk of rhabdomyolysis |

P450. This enzyme has a great number of isoenzymes, while more than 50 % of drugs are metabolized by CYP3A4 isoenzyme. Xenobiotics that are capable of inhibiting or inducing the enzymes of the cytochrome P450, can markedly slow down or accelerate the metabolism of other drugs that are metabolized by the corresponding enzyme. From the clinical point of view inhibition is more dangerous, because its effect appears very quickly after application of the corresponding inhibitor. Consequences of enzyme induction are manifested substantially later, when drug metabolism acceleration occurs due to significantly increased synthesis of the corresponding enzyme. After discontinuation of the enzyme inductor, activity of induced enzymes decreases to the baseline values within 1 to 3 weeks (Micuda et al, 1998).

Antimicrobial agents that inhibit CYP3A4 isoenzyme are especially macrolide antibiotics (erythromycin and troleandomycin are the strongest inhibitors, clarithromycin is weaker, and azithromycin and dirithromycin do not inhibit CYP3A4), azole antimycotics (above all ketoconazole and itraconazole); of antiviral agents it is a non-nucleoside inhibitor of reverse transcriptase delavirdine and inhibitors of HIV proteases (indinavir, nelfinavir). This isoenzyme inhibition can cause a slow down of the metabolism of some drugs (Tab. 2), resulting in manifestations of their toxicity. Fluorinated quinolones (ciprofloxacin, enoxacin, less norfloxacin) inhibit CYP1A, leading in this way to the increase of theophylline level in plasma (Gregg, 1999; Nahata, 1996; Niki et al, 1992).

The most important inductors of cytochrome P450 enzymes among antimicrobial agents are rifamycins (rifampicin and rifabutin). Enzyme induction is manifested by decreasing levels, weakening and shortening the effects of simultaneously administered drugs, namely: corticosteroids, oral contraceptives, warfarin, derivatives of sulfonylurea, verapamil, metoprolol, cyclosporine, itraconazole, ketoconazole, theophylline, phenytoin, isoniazid and others (Gregg, 1999; Hafner et al, 1998).

Adverse effects and interactions belong to the most frequent causes of treatment failures. Many of them are preventable. Knowledge of reasons and ready monitoring of patients can decrease the occurrence of adverse effects. Perception of adverse effects is one of the markers of drug therapy quality. Antibiotics took the second place as to the number of reported drug adverse effects in Slovakia in the year 2001. This fact suggests a high rate of prescription, being frequently unreasonable, since antibiotics are regarded as a relatively safe drug group.

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Received February 14, 2002.
Accepted June 20, 2002.