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SIDE EFFECTS OF ANTI-TUBERCULOSIS DRUGS

Djumaev Mukhtor Fatullaevich
Bukhara State Medical Institute, Head of the Department of Phthisiology and Pulmonology, Associate Professor, PhD
Jumayev.muxtor@bsmi.uz

Abstract: Chemotherapy of tuberculosis, especially multidrug-resistant forms, remains a complex task due to the development of adverse reactions (ADRs), which often lead to non-compliance with the treatment regimen, its discontinuation and, as a consequence, to the growth of drug resistance of Mycobacterium Tuberculosis . Second-line drugs are the most toxic. This review systematizes the main types of side effects of anti-tuberculosis drugs, examines the pathogenetic mechanisms of their development, and discusses modern approaches to prevention and treatment, including pharmacological and non-pharmacological methods.
Key words : tuberculosis, anti-tuberculosis drugs, side effects, hepatotoxicity, neurotoxicity, correction, drug resistance.

Introduction. Effective control of tuberculosis (TB) is impossible without long-term and complex chemotherapy. Standard treatment regimens, including first-line drugs (isoniazid, rifampicin, pyrazinamide, ethambutol), as well as more potent and toxic second-line drugs (e.g., amikacin, capreomycin, fluoroquinolones, cycloserine, prothionamide) are associated with a wide range of adverse reactions [1]. The high frequency of ADRs is one of the key reasons for decreased treatment adherence, which contributes to the selection of resistant mycobacterial strains and the development of drug-resistant tuberculosis (DR-TB) [2]. In this regard, timely diagnosis, prevention and effective management of side effects are an integral part of successful anti-tuberculosis therapy.

1. Main types of side effects and mechanisms of their development

1.1 Hepatotoxicity

Hepatotoxicity is the most common and dangerous complication of first-line therapy. Isoniazid , rifampin, and pyrazinamide have a direct toxic effect on hepatocytes .

Isoniazid metabolized in the liver to form hepatotoxic hydrazones . Patients with the "fast" type of acetylation have a higher risk of liver damage [3].

Pyrazinamide induces hepatitis by disrupting mitochondrial function and ATP synthesis.

Rifampicin , being a potent inducer of cytochrome P450, can potentiate the toxicity of isoniazid metabolites [4].

Clinically, this is manifested by an increase in the level of transaminases (ALT, AST), in severe cases – jaundice, symptoms of liver failure.

1.2. Neurotoxicity

Neurotoxic effects include peripheral neuropathy , seizures, psychosis, depression.

Isoniazid causes a deficiency of vitamin B6 (pyridoxine), which is a cofactor in the synthesis of GABA, the main inhibitory neurotransmitter in the central nervous system. GABA deficiency leads to seizures, and peripheral nerve damage leads to neuropathy [5].

Cycloserine is an NMDA receptor antagonist, which can cause a wide range of psychiatric symptoms, from dizziness and tremors to psychosis and suicidal ideation [6].

Fluoroquinolones (levofloxacin , moxifloxacin) are associated with the development of insomnia, headache, and in rare cases, seizures and peripheral neuropathy .

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1.3. Nephrotoxicity and ototoxicity

These effects are typical for second-line injectable drugs – aminoglycosides (amikacin , kanamycin) and the polypeptide capreomycin .

Nephrotoxicity is manifested by an increase in the level of creatinine and urea in the blood, the development of acute renal failure due to damage to the renal tubular apparatus [7].

Ototoxicity involves irreversible damage to the hair cells of the cochlea and vestibular apparatus, leading to permanent hearing loss and balance disorders [8].

1.4 Gastrointestinal disorders

Nausea, vomiting, abdominal pain, and diarrhea are common side effects of many anti-tuberculosis drugs, especially rifampin , pyrazinamide , and prothionamide . The mechanisms are related to direct irritation of the gastrointestinal mucosa and disruption of the microflora.

1.5. Other side effects

Arthralgia and hyperuricemia : caused by pyrazinamide , which competitively inhibits uric acid excretion.

Skin reactions: from mild rash to severe Stevens -Johnson syndrome (more often associated with isoniazid).

Visual impairment (retrobulbar neuritis): a characteristic side effect of ethambutol , dose-dependent and usually reversible [9].

2. Strategies for the elimination and prevention of side effects

2.1 General principles

Patient education: information about possible ADRs and the need to report them promptly to the physician.

Active monitoring: regular monitoring of biochemical (ALT, AST, bilirubin, creatinine , uric acid) and clinical parameters (assessment of hearing, vision, neurological status) [10].

Rationalization of the chemotherapy regimen: use of less toxic analogues (for example, bedaquiline instead of injectable drugs for DR-TB), dose adjustment in case of renal or hepatic insufficiency.

2.2. Pharmacological correction of specific ADRs

Hepatotoxicity :

Prevention: administration of hepatoprotectors (essential phospholipids, ademetionine) to patients at risk.

Treatment: in case of moderate increase in transaminases (3-5 times higher than normal) – dose adjustment, increase in hepatoprotective therapy. In case of severe hepatotoxicity – temporary discontinuation of all hepatotoxic drugs followed by their gradual reintroduction under strict control [4].

Neuropathy and other neurological disorders:

Prevention: mandatory administration of pyridoxine (vitamin B6) at a dose of 25-50 mg/day to all patients receiving isoniazid or cycloserine [5].

Treatment: If neuropathy develops , increase the pyridoxine dose to 100-200 mg/day. For psychiatric reactions to cycloserine , prescribe anxiolytics , antidepressants, and antipsychotics; in severe cases, temporarily discontinue the drug.

Nephro- and ototoxicity :

Prevention: careful selection of the dose of aminoglycosides taking into account renal function, monitoring of serum concentrations (therapeutic drug monitoring), regular audiometry.

Treatment: At the first sign of toxicity, replace the injectable drug with an oral one (e.g., linezolid , bedaquiline). There is no specific therapy for ototoxicity .

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Gastrointestinal disorders:
Taking medications during meals (unless otherwise indicated, such as for rifampicin , which should be taken on an empty stomach).
Prescription of prokinetics (domperidone), antispasmodics, antiemetics.
Arthralgia:
In case of hyperuricemia without clinical symptoms, no correction is required.
If gouty arthritis develops, nonsteroidal anti-inflammatory drugs (NSAIDs) and colchicine are prescribed. Allopurinol is rarely used.
Conclusion. Adverse reactions to anti-TB drugs pose a serious problem, threatening the success of treatment. Their effective management requires a comprehensive approach, including thorough pre-treatment screening, active follow-up, timely diagnosis of adverse reactions, and knowledge of treatment algorithms. The introduction of new, less toxic drugs (bedaquiline , delamanid) into DR-TB treatment regimens offers new opportunities to reduce the burden of adverse reactions and improve treatment outcomes. However , proper management of adverse reactions remains a cornerstone of the TB physician's work.

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