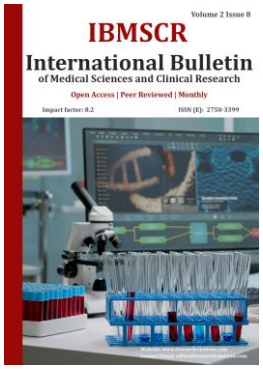

NEUTROTOXIC SIDE EFFECTS OF ANTITUBERCULOUS DRUGS

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https://doi.org/10.5281/zenodo.7931820

Abstract. Data from 36 literature sources on the neurotoxic properties of anti-tuberculosis drugs, their clinical manifestations and mechanisms of neurotoxic action were analyzed. Predisposing factors to the development of neurotoxicity and risk groups have been identified. The necessity of early detection of neurotoxicity of chemotherapy regimens for timely correction and full treatment of patients is substantiated.

Keywords: adverse reactions, anti-tuberculosis drugs, neurotoxicity, method.

INTRODUCTION

In the structure of adverse events that occur during chemotherapy in patients with tuberculosis, the frequency of neurotoxic reactions varies in a wide range - from 11-12% [2] to 24-26% [1, 11] and 50.8% [4]. Such a scatter of data is due, on the one hand, to a wide range of side effects on the part of the nervous system, and on the other hand, to the safety profile of drugs included in chemotherapy regimens and various mechanisms of action on the nervous system.

MATERIALS AND METHODS

Neurotoxicity is a common occurrence with drugs from many therapeutic classes, especially antimicrobials. Manifestations of neurotoxicity range from ototoxicity, visceral neuropathy, and neuromuscular blockade (lesion of the peripheral nervous system) to impaired consciousness, nonspecific encephalopathy, seizures, and nonconvulsive status epilepticus (damage to the central nervous system) [2]. Predisposing factors for the development of neurotoxicity are the ability of drugs to penetrate the central nervous system (CNS), which is determined by the state of the blood-brain barrier and the lipophilicity of the drug. The likelihood of drug neurotoxicity is increased by renal and/or hepatic insufficiency with impaired drug elimination, a burdened history of neuropsychiatric diseases, and the elderly age of patients [3].

RESULTS AND DISCUSSION

Drugs used for the treatment of tuberculosis are characterized by the whole spectrum of neurotoxic reactions, which can manifest themselves in the form of disturbances in motor and sensory functions (impaired hearing, vision), emotional status, and integrative functions of the brain, such as memory, learning.

The most common damage to the nervous system in newly diagnosed patients with tuberculosis is recorded when taking isoniazid, it can be manifested by headache, dizziness, sleep disturbance, neuritis or atrophy of the optic nerve, peripheral polyneuritis, muscle twitching and convulsions [4]. A special form of encephalopathy, characteristic of isoniazid, has been described, in which symptoms occur weeks and even months after the start of the drug, and is manifested mainly by the development of psychosis with changes in the electroencephalogram. Isoniazid has the greatest potential for peripheral neurotoxicity. Often

developed neurotoxic reactions require the abolition of isoniazid. Thus, according to, isoniazid was discontinued in 13.3% of patients due to toxic reactions from the CNS and in 11.5% from the peripheral nervous system. The review [2] describes in detail the proven mechanisms of action of isoniazid, which lead to disruption of the processes of excitation and inhibition in the CNS, and possible ways to correct its toxic effect.

The neurotoxicity of cycloserine can be manifested by visual impairment, polyneuritis, headache, dizziness, sleep disturbance, dysarthria, disorientation, accompanied by memory loss, psychosis, attacks of clonic convulsions.

Optic neuropathy is a known neurotoxic manifestation with ethambutol. Optic neuropathy is thought to be secondary to ethambutol-induced mitochondrial dysfunction. Pathological studies revealed demyelinating lesions of the optic nerve and chiasm in patients with ethambutol-induced optic neuropathy.

The most common neurotoxic effect associated with aminoglycosides is ototoxicity (toxic effect on the inner ear, as well as on the vestibulocochlear nerve), due to the increased concentration of these drugs in the fluids of the inner ear and their long elimination time. As a result of cochleotoxic action, chronic sensorineural hearing loss of varying severity develops; in the case of a vestibulotoxic effect, a persistent imbalance may persist for several years, which is hardly amenable to therapeutic effects. All aminoglycosides, to one degree or another, have both vestibulo- and cochleotoxicity. At the same time, the use of streptomycin often causes vestibular disorders, while kanamycin and amikacin worsen hearing to a greater extent [2]. The analysis of clinical observations carried out by the authors showed that the following factors influence the development of ototoxicity: the dose and duration of the drug; kidney disease with impaired excretory function, including as a result of the direct nephrotoxic action of the aminoglycoside; simultaneous administration of an aminoglycoside and loop diuretics, which accelerate the penetration of the aminoglycoside into the endolymph; the simultaneous appointment of an aminoglycoside and another ototoxic drug. One of the likely mechanisms of ototoxicity is excitotoxic activation of NMDA receptors in the cochlea, which can lead to oxidative stress and cell death. The study [3] found that the mechanism of development of ototoxicity involves the disruption of mitochondrial protein synthesis in the hair cells of the inner ear by aminoglycosides.

In addition to ototoxicity, other disorders are known, such as peripheral neuropathy, encephalopathy, and neuromuscular blockade, which is based on presynaptic inhibition of the quantitative release of acetylcholine at the neuromuscular junction and the binding of aminoglycosides to the acetylcholine complex. Receptors, followed by calcium depletion. Neurotoxic complications of aminoglycosides are more common in patients with increased CNS permeability. Initially, neuromuscular blocking effects were established in patients with tuberculosis using streptomycin, and then found in amikacin and kanamycin [2].

Over the past decade, new aspects of the safety profile of fluoroquinolones have been identified. Previously, CNS side effects such as insomnia, headache, dizziness, nervousness, and restlessness were the most common (1 to 6%), which usually resolve after discontinuation of the drug, while epileptic seizures and psychoses were rare (0.2 to 2%) [3]. Recent studies have shown that fluoroquinolones may be more frequently associated with delirium and psychosis than previously thought. In 2018, the US Food and Drug Administration (FDA), based on an analysis of spontaneous reports entered into the FDA database, concluded that for fluoroquinolones class adverse drug reactions are hypo-

glycemia and mental disorders: attention disorders, disorientation, agitation, nervousness, memory loss, delirium [1]. According to the database of the National Center for Pharmacovigilance of France], out of 590 reports of the development of neuropsychiatric disorders, confusion was indicated in 51% of cases, hallucinations in 27%, agitation in 13%, and delirium in 12%. , and in 21.7% of cases, neurotoxic reactions were classified as serious patients requiring hospitalization. Disorders of the CNS activity were observed with the use of all known oral fluoroquinolones, mainly in the elderly (mean age of patients 66 years). The data of the Russian national database of spontaneous reports registered by Roszdravnadzor were analyzed. Of the 57 reports of mental disorders, depression and hallucinations (15 and 14 cases), anxiety and acute psychosis (6 and 5 cases) predominated. Levofloxacin was listed as a suspected fluoroquinolone in 20 cases, moxifloxacin in 9 cases, ofloxacin in 8 cases, and ciprofloxacin in 7 cases. Most often, neuropsychiatric disorders developed during the first 10 days of taking fluoroquinolones, with 14 out of 28 patients on the first day of treatment. In most cases, the withdrawal of the suspected fluoroquinolone was accompanied by relief of all symptoms or a pronounced improvement in the patient's well-being. The mean age of the patients was 44.4 years.

CONCLUSION

Neurotoxic AEs caused by anti-TB drugs can have many neurological manifestations. Patients with pre-existing central and peripheral nervous system disease, renal insufficiency, and advanced age may be particularly vulnerable. Another important factor to consider is the concomitant use of several drugs with neurotoxic and/or nephrotoxic effects. This situation is typical for the treatment of TB patients with MDR/XDR MBT. Early diagnosis of neurotoxic manifestations in chemotherapy regimens is necessary for their symptomatic correction and development of prevention methods in order to provide a full-fledged treatment of tuberculosis.

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