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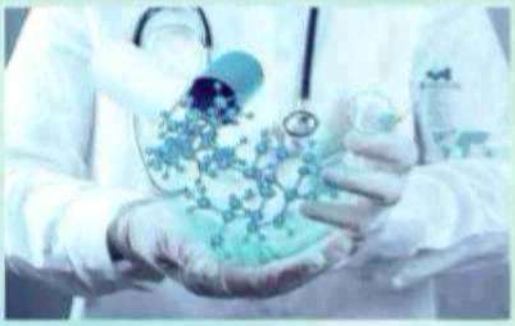

AVICENNA-MED.UZ

ISSN 2181-712X.
EiSSN 2181-2187

5 (79) 2025

ТИББИЁТДА ЯНГИ КУН
НОВЫЙ ДЕНЬ В МЕДИЦИНЕ
NEW DAY IN MEDICINE

Илмий-рефератив, маънавий-маърифий журнал
Научно-реферативный,
духовно-просветительский журнал

УЧРЕДИТЕЛИ:

БУХАРСКИЙ ГОСУДАРСТВЕННЫЙ МЕДИЦИНСКИЙ ИНСТИТУТ
ООО «ТИББИЁТДА ЯНГИ КУН»

Национальный медицинский исследовательский центр хирургии имени А.В. Вишневского является генеральным научно-практическим консультантом редакции

Журнал был включен в список журнальных изданий, рецензируемых Высшей Аттестационной Комиссией Республики Узбекистан (Протокол № 201/03 от 30.12.2013 г.)

5 (79)

2025

май

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Received: 20.04.2025, Accepted: 06.05.2025, Published: 10.05.2025

УДК 616-2.5-572.7.06:616.155.194.8

CLINICAL EFFICACY OF THIAZIDE IN THE TREATMENT OF MDR PULMONARY TUBERCULOSIS

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✓ ***Resume***

Thiotriazoline (trade name) is known under the international nonproprietary name (INN) as " morpholinium salt of thiazide acid" or simply " thiazotic acid". is a domestic drug with membrane-stabilizing, anti-ischemic, antioxidant and immunomodulatory effects. In clinical practice, it is known as a hepatoprotector and cardioprotector . Thiotriazoline activates the body's antioxidant systems and inhibits lipid peroxidation, improves energy metabolism in cells under hypoxic conditions. Previously, the anti-inflammatory and organoprotective effect of thiotriazoline in patients with tuberculosis was reported. These properties served as the basis for attempts to use thiotriazoline as a pathogenetic agent for pulmonary tuberculosis. It is expected that the addition of an antioxidant to therapy will increase the clinical effectiveness of treatment and reduce the incidence of complications.

Keywords: Thiotriazoline, hypoxia, granuloma, lung tissue, antioxidant.

MULTIDORILARGA CHIDAMLI O'PKA TUBERCULOSIS DAVOLASHDA TIAZID KISLOTANING KLINIK SAMARADORLIGINI BAHOLASH

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✓ ***Rezyume***

Tiotriazolin (savdo nomi) xalqaro nodavlat nomi (INN) ostida "tiazid kislotasining morfoliniy tuzi" yoki oddiygina "tiazotik kislota" sifatida tanilgan. membrananing barqarorlashtiruvchi, ishemikga qarshi, antioksidant va immunomodulyatsion ta'sirga ega mahalliy davo vosita. Klinik amaliyotda u gepatoprotektor va kardioprotektor sifatida tanilgan. Tiotriazolin organizmning antioksidant tizimlarini faollashtiradi va lipid peroksidatsiyasini inhibe qiladi, gipoksik sharoitda hujayralardagi energiya almashinuvini yaxshilaydi. Ilgari, sil bilan og'rigan bemorlarda tiotriazolinning yallig'lanishga qarshi va organoprotektiv ta'siri haqida xabar berilgan edi. Bu xususiyatlar tiotriazolinni o'pka tuberkulyozining patogenetik agenti sifatida ishlatishga urinishlar uchun asos bo'lib xizmat qildi. Terapiyaga antioksidant qo'shilishi davolashning klinik samaradorligini oshirishi va asoratlarni kamaytirishi kutilmoqda.

Kalit so'zlar: Tiozat kislota, gipoksiya, granuloma, o'pka to'qimasi, antioxidant

ОЦЕНКА КЛИНИЧЕСКОЙ ЭФФЕКТИВНОСТИ ТИАЗИДНОЙ КИСЛОТЫ В ЛЕЧЕНИИ ТУБЕРКУЛЕЗА ЛЕГКИХ С МНОЖЕСТВЕННОЙ ЛЕКАРСТВЕННОЙ УСТОЙЧИВОСТЬЮ

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✓ ***Резюме***

Тиотриазолин (торговое название) известен под международным непатентованным наименованием (МНН) как «морфолиниевая соль тиазидовой кислоты» или просто «тиазотовая кислота». — отечественный мембраностабилизирующим, противоишемическим, антиоксидантным и иммуномодулирующим действием. В клинической практике известен как гепатопротектор и кардиопротектор. Тиотриазолин активирует антиоксидантные системы организма и ингибирует перекисное окисление липидов, улучшает энергетический обмен в клетках в условиях гипоксии. Ранее сообщалось о противовоспалительном и органопротекторном действии тиотриазолина у больных туберкулезом. Эти свойства послужили основанием для попыток использования тиотриазолина в качестве патогенетического средства при туберкулезе легких. Ожидается, что добавление антиоксиданта к терапии позволит повысить клиническую эффективность лечения и снизить частоту осложнений.

Ключевые слова: Тиотриазолин, гипоксия, гранулема, легочная ткань, антиоксидант.

Introduction

Multidrug resistance of the tuberculosis pathogen (MDR-TB) is a serious problem in phthisiology, significantly reducing the effectiveness of standard chemotherapy. Millions of new cases of tuberculosis are registered annually, and the mortality rate from it exceeds 1.5 million people per year. The COVID-19 pandemic has worsened the situation by interrupting many anti-tuberculosis programs, which has led to an increase in tuberculosis morbidity and mortality. In Uzbekistan and other countries with a high TB burden, epidemiological indicators remain alarming. Standard treatment regimens for MDR-TB require a long-term combination of second-line drugs, which themselves often cause severe side effects (hepatotoxicity, nephrotoxicity, etc.). A significant proportion of patients have impaired immune status and homeostasis system, contributing to the progression of inflammation. Oxidative stress plays a major role in the pathogenesis of tuberculosis: excessive free-radical oxidation damages lung tissue and maintains chronic inflammation. Increased lipid peroxidation is detected in destructive forms of TB and correlates with the severity of the inflammatory reaction. These facts justify the use of antioxidants in the complex therapy of tuberculosis.

The aim of the study: to evaluate the clinical efficacy and tolerability (safety) of thiotriazoline in the complex treatment of patients with MDR pulmonary tuberculosis.

Materials and methods

Study design: prospective comparative clinical study (controlled non-randomized). The study included 142 patients with confirmed pulmonary tuberculosis with MDR, treated at the Bukhara Regional Center for Phthisiopulmonology and the Republican Specialized Scientific and Practical Center for Phthisiopulmonology in 2020-2023 . Inclusion criteria: bacteriologically verified pulmonary tuberculosis with multiple (or extensively) drug resistance of mycobacteria, age 18-75

years, informed consent. Patients younger than 18 or older than 75 years, with severe decompensated concomitant diseases, HIV infection, generalized forms of tuberculosis, pregnant and lactating women, as well as those requiring emergency surgical care were not included. All participants received approval from the local ethics committee, treatment was carried out in compliance with the principles of bioethics.

Therapy groups: The main group included 81 patients who received standard anti-tuberculosis chemotherapy in combination with thiotriazoline . The control group included 61 patients who received only standard chemotherapy. The groups were comparable by gender and age: 71.6% men in the main group and 72.1% in the control group; the average age was 45.2±2.1 and 46.0±2.4 years, respectively ($p>0.05$). The differences in the form of tuberculosis were statistically insignificant (the proportion of primary and secondary TB was similar). Standard chemotherapy was selected individually according to national protocols and included at least 4–5 second-line anti-tuberculosis drugs in the intensive phase. Thiotriazoline was prescribed additionally: the first 2 weeks - intravenous drip of 100 mg daily, then orally 100 mg 3 times a day for up to 2 months of the course. The total duration of thiotriazoline administration was 60 days during the intensive therapy phase.

Efficacy assessment: Patients were observed in hospital during the intensive phase (2 months). The analysis of clinical symptoms (intoxication, cough, dyspnea, etc.), body weight dynamics, laboratory markers of inflammation (ESR, C-reactive protein), respiratory function and gas exchange, radiographic indicators (resorption of infiltrates, closure of caverns) was performed. Bacteriological efficacy was assessed by cessation of bacterial excretion (negative smear and sputum culture). Tolerability of therapy was assessed by the frequency and severity of adverse reactions, especially hepatotoxic (liver reactions were monitored by the levels of ALT , AST). The criterion for cure was clinical and bacteriological recovery with closure of decay cavities (if necessary, after surgery).

Research methods: General clinical studies (blood and sputum tests), biochemical monitoring of liver function, spirometry, and arterial blood gas analysis were performed at the beginning of treatment and after 1 and 2 months of therapy. Chest X-ray was performed monthly, and CT was performed if necessary. Complications of treatment were recorded daily. SPSS 23.0 package was used for statistical processing; quantitative data are presented in M±m format . The groups were compared using Student's t-test and χ^2, differences were considered reliable at $p< 0.05$.

Result and discussions

Clinical dynamics. The addition of thiotriazoline provided accelerated clinical improvement compared to standard therapy. Already after 1 month from the start of treatment, 67 patients of the main group (82.7%) showed a significant reduction in intoxication symptoms (normalization of temperature, appetite, sleep) and cough syndrome, while in the control group such improvement was observed only in 45 patients (73.8%). By the end of the 2nd month of therapy, clinical recovery (almost complete disappearance of symptoms) was achieved in 81.5% of patients of the main group versus 34.4% in the control. Patients of the main group gained weight faster: over 2 months, the average weight gain was +3.5±0.5 kg, while in the control +1.8±0.4 kg ($p< 0.05$). More active restoration of mass indicates an improvement in trophic status and a decrease in chronic intoxication against the background of thiotriazoline .

Respiratory function and gas exchange. After 2 months of treatment, the vital capacity of the lungs (VC) in the main group increased from 68.5±2.3% to 81.2±2.0% of the predicted value (an increase of ~13%), while in the control group it increased from 69.1±2.5% to 75.0±2.2% (an increase of ~6%; the difference between the groups is reliable, $p< 0.05$). Maximum ventilation of the lungs also increased more in those receiving thiotriazoline . Normalization of the gas composition of arterial blood ($PaO_2 > 80$ mm Hg , $PaCO_2$ 35–45 mm Hg) by the end of the 2nd month was achieved in 55.6% of patients in the main group, which is three times higher than in patients without thiotriazoline (16.4%). Moreover, after just 1 month of therapy, the number of patients with normal gas parameters was significantly higher in the main group: 18.5% versus only 3.3% in the control. Thus, against the

background of antioxidant support, a faster restoration of gas exchange and a decrease in respiratory failure were noted (these data are analyzed in more detail in the third article).

Radiographic dynamics. By the end of the intensive treatment phase, most patients in the main group showed significant positive radiographic transformation. Complete resorption of infiltrative changes in the lungs or their significant reduction over 2 months was noted in 79% of patients with thiotriazoline versus fifty % of patients in the control ($p < 0.01$). Spontaneous closure of cavities (without surgery) by the 2nd month was achieved in 74.1% of patients in the main group, which is 2.3 times higher than in the control (about 32 %). Accordingly, the need for surgical intervention arose significantly less frequently: only 12 patients (14.8%) of the main group required surgery, while in the control - 40 patients (65.6 %) . Large cavities requiring lung resection more often persisted in the control group, which explains the high frequency of operations in the absence of thiotriazoline . Thus, the use of thiotriazoline contributed to the accelerated healing of specific cavities and a decrease in the volume of residual changes in the lungs.

Bacteriological efficacy. The main group demonstrated earlier and higher negativity of sputum. After 1 month of treatment, cessation of bacterial excretion (negative smear and culture) was achieved in 54.3% of patients with thiotriazoline , while in the control group – only in 26.2%. By the end of the 2nd month, the proportion of patients with negative sputum was 90.1% in the main group versus 68.9% in the control ($p< 0.01$). Moreover, in the main group there was not a single case of relapse of bacterial excretion after the initial conversion, while in the control, several patients showed repeated appearance of mycobacteria in sputum during continued treatment. Thus, thiotriazoline ensured more reliable and rapid bacteriological conversion, improving epidemiological safety (infection of others ceased earlier).

Laboratory markers of inflammation. The dynamics of the systemic inflammatory response also differed between the groups. The erythrocyte sedimentation rate (ESR) decreased from 35±3 to 10±2 mm/hour in patients of the main group over 2 months, while in the control group it decreased from 34±4 to 18±3 mm/ hour. Normalization of ESR (≤15 mm/hour) was achieved in 90% of patients of the main group versus 60% in the control by the end of the intensive phase. The level of C-reactive protein (CRP) in the main group decreased from ~48 mg/l to 6 mg/l after 1 month of therapy, while in the control group it remained elevated (~20 mg/l) by the same time. These indicators confirm a more rapid attenuation of the inflammatory process against the background of antioxidant therapy.

Tolerability of treatment. The use of thiotriazoline significantly improved the tolerability of anti-tuberculosis chemotherapy. In the control group, 24.6% of patients (15 of 61) showed a significant increase in transaminases (ALT > 100 U / l) in the second month due to drug-induced hepatitis; in 5 patients, it was necessary to temporarily discontinue pyrazinamide . In the main group, a similar increase in ALT > 100 U / l was observed only in 3 patients (3.7 %) . The average ALT / AST values after a month of treatment in the group without thiotriazoline were 48/45 U / l, while with thiotriazoline - 30/28 U / l. By the end of the 2nd month, almost all patients in the main group normalized liver function tests, while in the control, some retained deviations requiring hepatoprotectors. Thus, the frequency and severity of hepatotoxic reactions were significantly lower when using thiotriazoline . In the main group, no cases of severe drug-induced hepatitis were recorded (0% versus 6.6% in the control). Also, in the main group, there were no fatal outcomes, while in the control group, 2 cases of death from tuberculosis progression were noted (despite the operations). All patients in the main group were able to complete a full course of chemotherapy without forced interruptions, while in the control, 8.2% of patients prematurely stopped treatment due to complications.

Discussion

The obtained results showed that the addition of thiotriazoline to the therapy of MDR pulmonary tuberculosis significantly increases the effectiveness of treatment and improves its tolerability. Achieving bacteriological conversion and closure of cavities occurred at an earlier time and in a larger

number of patients, which is consistent with the concept of pathogenetic therapy with protection of lung tissue from damage. The antioxidant and membrane-protective effect of thiotriazoline probably leads to a decrease in the destruction of the pulmonary parenchyma and acceleration of reparative processes, which was morphologically confirmed in our study (see the second article). This ensures a more rapid restoration of the structure and function of the lungs after treatment . As a result, the risk of residual cavities and the need for extensive surgeries is reduced, which is especially important in MDR tuberculosis. In the main group, only 14.8% of patients required surgery versus 65.6% in the control group, that is, most patients treated with thiotriazoline managed to avoid surgery thanks to successful conservative therapy.

A significant reduction in the hepatotoxicity of anti-tuberculosis treatment in patients receiving thiotriazoline confirms the previously known hepatoprotective properties of this drug. Our data are consistent with the results of Shovkun et al . (2013) and Sedov (2015), who reported the ability of thiotriazoline to prevent drug-induced hepatitis during tuberculosis chemotherapy . Due to this, patients in the main group could continuously receive a full course of treatment without interruptions, which is extremely important for cure and prevention of resistance development . In contrast, in the control group, forced interruptions and drug withdrawals due to side effects worsened outcomes. Thus, thiotriazoline not only enhances the anti-tuberculosis effect, but also makes treatment safer and more controllable.

Our results correlate well with the data of other studies. In particular, Kuznetsova (2020) noted in clinical experience that the use of thiotriazoline in patients with tuberculosis increases the effectiveness of therapy and improves tolerability. Gorbachev (2016) pointed out the positive clinical effects of thiotriazoline in the complex therapy of TB associated with its immunomodulatory effect. A previous study by Arkhipova (2014) demonstrated that thiotriazoline normalizes the cytokine profile in tuberculosis patients, reducing excessive proinflammatory stimulation. This is consistent with our observation of a more rapid decrease in systemic inflammation (ESR, CRP) under the influence of an antioxidant. In addition, we note the work of Maksimov (2021), who emphasized the promise of antioxidant therapy in the treatment of tuberculosis. Our study supplemented this information with specific quantitative indicators and morphological evidence of the effectiveness of thiotriazoline .

It is important to emphasize that even against the background of thiotriazoline, the most severe patients with massive destruction still required surgical care (approximately 15% of cases). This indicates that pathogenetic therapy does not cancel traditional approaches, but complements them. However, a significantly smaller proportion of those operated on in the main group shows that timely activation of antioxidant protection can save many patients from traumatic operations. It should also be noted that there were no fatal outcomes in the main group versus cases of disease progression in the control group - an indirect sign of a more controlled course of tuberculosis when using thiotriazoline .

Overall, the combined use of thiotriazoline with anti-tuberculosis drugs has allowed for faster and more complete clinical cure while minimizing the harm from the therapy itself. This makes this approach extremely valuable from a medical and social point of view. Patients not only get rid of the infection faster, but also restore their health with fewer losses, which accelerates their return to work and reduces disability . Earlier cessation of bacterial excretion increases epidemiological safety. Good tolerability strengthens adherence to treatment, reducing the risk of its interruption. All this together improves outcomes in such a severe disease as MDR-tuberculosis.

Limitations of the study: the lack of randomization and placebo control reduces the strength of the evidence, but the homogeneity of the groups and statistically significant differences in key indicators allow for confident interpretation of the results. Further studies with longer follow-up are desirable in order to assess remote results (relapse rate, lung function after a year or more).

Conclusion

The use of thiotriazoline in the complex therapy of MDR pulmonary tuberculosis significantly increases the clinical efficacy of treatment and improves its tolerability. Additional antioxidant support led to accelerated resorption of infiltrates and closure of cavities, earlier bacteriological conversion of sputum and, ultimately, to an increase in the frequency of complete recovery without surgery (81.5% versus 34.4% in the control). Against the background of thiotriazoline , a decrease in the frequency of

chemotherapy complications was noted, primarily drug-induced hepatitis (0% versus 6.6% of severe hepatotoxic reactions), which made it possible to carry out treatment without forced pauses. In the main group, there were no fatal outcomes, whereas with standard treatment, a number of severe patients experienced disease progression.

Practical significance: inclusion of thiotriazoline in the treatment regimen for MDR pulmonary tuberculosis is advisable to increase the chances of successful cure and reduce the risk of toxic complications of therapy. This approach allows to reduce the duration of inpatient treatment (in our study - by ~17 days) and reduce the need for surgical lung resections (our data: 14.8% versus 50.8% of patients), which is economically and socially beneficial. The obtained results served as the basis for recommendations for the introduction of thiotriazoline into the wide clinical practice of phthisiology .

Scientific novelty: for the first time, a comprehensive study of the effect of thiotriazoline in MDR tuberculosis was conducted, including not only clinical and laboratory parameters, but also a morphological assessment of changes in the lung tissue. For the first time, it was proven that thiotriazoline accelerates the maturation of tuberculous granulomas and limits the area of specific inflammation with a connective tissue capsule (morphological substantiation of the effect). What is new is the confirmation of the improvement of functional parameters of respiration and gas exchange under the influence of antioxidant therapy. Thus, fundamentally new data on the pathogenetic effect of thiotriazoline in tuberculosis were obtained, expanding the understanding of the possibilities of optimizing the treatment of severe forms of TB.

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Entered 20.04.2025