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CLINICAL EFFICIENCY OF SODIUM SELENITE IN TREATMENT OF TUBERCULOSIS PATIENTS WITH AUTOIMMUNE THYROIDITIS

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Резюме. Клиническая эффективность селенита натрия в лечении больных туберкулезом с аутоиммунным тиреоидитом.

Цель работы — изучить эффект препарата селена на тиреоидный статус и исходы химиотерапии больных деструктивным туберкулезом легких с аутоиммунным тиреоидитом. *Материалы и методы.* Эффект селена на тиреоидный статус и исходы химиотерапии изучали при наблюдении за 180 больными туберкулезом с патологическими структурными изменениями щитовидной железы. Из них 3 подгруппы наблюдения получали натрия селенит в течение первых 2 мес. стандартной химиотерапии, а 3 подгруппы контроля - только стандартную химиотерапию. В сыворотке венозной крови у всех пациентов до начала терапии и через 2 мес. после ее начала определяли иммуноферментативным методом уровни селена, свободного тироксина, тиреотропного гормона гипофиза, антител к тиреоглобулину и тиреопероксидазе. Кроме того, сравнивали эффективность лечения (процент прекращения бактериовыделения и заживления деструкций) в течение фазы интенсивной терапии. *Результаты и обсуждение.* У больных туберкулезом, в том числе в подгруппах с мультирезистентным процессом и ко-инфекцией туберкулез/ВИЧ, в сочетании с тиреопатиями установлен субклинический гипотиреоз, усугубляющийся на фоне противотуберкулезной химиотерапии. Назначение натрия селенита в интенсивную фазу лечения больных туберкулезом при сочетании с аутоиммунным тиреоидитом и субклиническим гипотиреозом или патологическим эутиреоидным синдромом приводило к учащению абациллирования на 6,66—20 % и заживления деструкций на 10 % при сравнении с контролем. *Выводы.* У больных туберкулезом в сочетании с аутоиммунным тиреоидитом натрия селенит восстанавливает функцию щитовидной железы и оптимизирует результаты химиотерапии. Селенит натрия может быть рекомендован в качестве препарата сопровождения при химиотерапии таких пациентов.

Ключевые слова: Туберкулез, щитовидная железа, селен, результаты химиотерапии.

Summary.

Objective — to study the effect of selenium on the thyroid status and chemotherapy outcomes of patients with cavitary pulmonary tuberculosis and thyroid pathology.

Materials and methods. Effect of selenium on thyroid status and chemotherapy outcomes was studied by observing the 180 patients with tuberculosis and autoimmune thyroiditis. Patients of these 3 subgroups of observations received selenium nitric during the first 2 months of standardized chemotherapy, and 3 control subgroups - only standardized chemotherapy. In the serum of venous blood in all patients prior to initiating therapy and at 2 months of its beginning content levels of selenium, free thyroxine, thyroid stimulating pituitary hormone, antibodies to thyreoglobulin and thyroid peroxidase were determined by of an ELISA method. In addition, cure rates (% of bacteriological and destruction healing) were compared during the phase of intensive therapy. *Results and discussion.* In patients with tuberculosis in combination with autoimmune thyroiditis, subclinical hypothyroidism or pathological euthyroid syndrome was established, aggravated against the background of antituberculosis chemotherapy. When included in the complex treatment of patients with tuberculosis with autoimmune thyroiditis sodium selenite, the function of the thyroid gland was restored. Assigning sodium selenite to the intensive phase of treating patients with tuberculosis when combined with autoimmune thyroiditis and subclinical hypothyroidism led to an increase in stopping of bacilli excretion by 6.66–20% and healing of destruction by 10% when compared with control. *Conclusions.* In patients with tuberculosis and autoimmune thyroiditis selenium nitric restored thyroid function and optimized the results of chemotherapy. Selenium nitric can be recommended as a drug accompaniment during chemotherapy for these patients.

Key-words: tuberculosis, thyroid, selenium, chemotherapy outcomes.

Despite some improvement in the situation with tuberculosis in Ukraine, it remains difficult and even prognostically unfavorable [10]. In the conditions of the epidemic, the deterioration of the pathomorphosis of tuberculosis, the spread of threatening rates of manifestations of drug resistance of mycobacteria

and co-infection of tuberculosis / HIV, an associated pathology worsening the running of tuberculosis is of great importance. Equally important is the relationship between endocrine and immune changes in the running of tuberculosis. According to modern notions, tuberculosis refers to interleukin-dependent immuno-

deficiency's, which is accompanied by pronounced changes in the cytokine network of the body. The role of thyroid hormones in the formation of cellular immunity is well known. Cells of the monocyte-macrophage system are activated by thyroid gland directly and indirectly. Thyroid pathology, in particular autoimmune thyroiditis with subclinical hypothyroidism, have been found to exacerbate the running of tuberculosis and adversely effects on the results of anti-TB chemotherapy [1,2,4-8]. Negative influence of the disturbed function of the thyroid gland on the consequences of anti-TB chemotherapy is associated with its effect on the state of cellular immunity [3,9]. One of the decisive factors in the normal functioning of the thyroid gland is its sufficient supply by selenium [12,13,17,18,20,21,23]. Selenium is necessary for the activation and metabolism of thyroid hormones, the elimination of endogenous and exogenous hydroperoxidases [11]. The source of selenium replenishment is food. However, soil and water in Ukraine as in other European countries for the last 100-200 years are characterized by low levels of selenium.

Objective: to study the effect of sodium selenite on thyroid state and the consequences of chemotherapy in patients with cavitary pulmonary tuberculosis with autoimmune thyroiditis.

Materials and methods. The study involved 180 patients with pulmonary tuberculosis and autoimmune thyroiditis aged from 18 to 67 years.

The average age of patients was 34.43 years. In the gender perspective, men prevailed - 87%. Observation was carried out in the conditions of the hospital of the regional anti-tuberculosis dispensary № 1 in Kharkov. The research was conducted within the framework of the research theme «Study of mechanisms and determination of markers of favorable and unfavorable running of tuberculosis» (State registration number 0113U002283). Autoimmune pathology of thyroid was confirmed by typical pathological changes of this organ which was established by ultrasound examination on the diagnostic apparatus SSF-240A manufactured by Toshiba Medical Systems.

The diffuse pathology of the thyroid gland with heterogeneity of its structure and the heterogeneity of acoustic density with hyperplasia of the gland, hypoplasia or without change in its volume prevailed, which is typical for autoimmune thyroiditis.

The patients were divided into 6 groups: the observation group 1a - patients with drug-sensitive tuberculosis with standardized chemotherapy (SCT) receiving selenium (TB + SCT + Se) and the comparison group 1b - patients with tuberculosis with SCT (TB + SCH) who did not receive selenium; observa-

tion group 2a - patients with TB / HIV co-infection with SCT (TB / HIV + SCT + Se) received selenium and comparison group 2a - patients with TB / HIV co-infection with SCT (TB / HIV + SSH); who did not receive selenium; observational group 3a - patients with multidrug resistant tuberculosis and individual chemotherapy (ICT) including ethinamind (or prothionamind) and PAS who received selenium (MRTB + ICT + Se) and comparison group 3b - multidrug-resistant tuberculosis with the same individual chemotherapy (ICT) including ethinamind (or prothionamind) STDs who did not receive selenium (MRTB + ICT).

All patients were examined before treatment and after 2 months of chemotherapy in accordance with the standards for monitoring tuberculosis patients during the treatment. Patients in the intensive phase of treatment had standardized chemotherapy, including rifampicin and patients with MRTB - individualized anti-TB chemotherapy, included ethionamide (prothionamide) and PAS/

Co-infection patients also received high-active antiretroviral therapy (HAART) regardless of the level of T-lymphocytes in the blood.

In the complex treatment of patients in the observation group, sodium selenite was included in the form of the drug cefacel (Cefak, Germany) with 200 micrograms per day per os for 2 initial months. The comparison groups did not receive the drug se

The levels of selenium (Se) were in the serum of venous blood in all patients before the start of the therapy and after 2 months of therapy in the Synevo laboratory on the Perkin Elmer Zeeman AAS 4110 analyzer. Levels of free thyroxine (T4 free), thyroid stimulating hormone (TSH), antibodies to thyroglobulin (a / t TG) and thyroperoxidase (a / t TPO) were measured in the serum of venous blood in all patients before the start of therapy and after 2 months of therapy by the immunoassay ELIZA method.

Biochemical parameters before and after 2 months of therapy were compared between the respective monitoring and control groups. In addition, the rates of treatment effectiveness (%of the stopping of bacterial excretion and healing of the cavities) were compared during the intensive phase of the treatment.

Statistical processing of the data obtained by the method of variation statistics using the standardized package of calculations Microsoft Excel XP. The probability of a divergence of averages was determined by the Student's t criterion. The critical level of significance (P) in checking statistical hypotheses was assumed to be 0.05.

Results and discussion. In patients with tuber-

Table 1

The function of the thyroid gland and the content of selenium in the blood in different groups of patients with tuberculosis before and after 60 days of integrated therapy

Groups	T4free (pmol/l)	TSH (IU / ml)	A/t to TPO (IU / ml)	A/t to TG (IU / ml)	Se (μg / l)
1a: TB+AIT +Se (n=30)	¹ 11,12±0,80	¹ 4,30±1,20	¹ 42,64±2,72	¹ 16,88±1,39	¹ 66,2 ±8,30
	² 13,32±0,78	² 2,12±0,90	² 4,32±0,14*	¹ 16,88±1,39*	² 95,39±8,45*
1b: TB+AIT (n=30)	¹ 11,21±0,67	¹ 4,00±1,41	¹ 38,54±1,27	¹ 18,54±1,83	¹ 66,36±9,93
	² 8,12±0,80**	² 4,80±1,52**	² 43,22±1,65**	² 21,54±1,18**	² 68,50±5,35**
2a: TB/HIV+ AIT+Se (n=30)	¹ 9,89±1,20	¹ 3,12±0,34	¹ 31,12±4,34	¹ 30,30±4,48	¹ 63,27±10,79
	² 12,97±0,76*	² 1,87±0,23*	² 2,12±0,21*	² 4,03±3,66	² 94,69±9,52*
2b: TB/HIV+ AIT (n=30)	¹ 10,00±0,93	¹ 3,43±0,13	¹ 7,88±3,91	¹ 29,81±3,87	¹ 64,01±9,43
	² 10,37±1,01	² 4,12±0,61	² 6,77±4,11	² 30,12±5,12**	² 68,20±8,92**
3a: MRTB+ AIT+Se (n=30)	¹ 10,22±1,15	¹ 1,44±0,79*	¹ 4,77±0,38	¹ 3,13±1,05	¹ 56,66±6,89
	² 14,34±0,94*	² 1,29±0,05	² 3,76±0,81*	² 2,25±1,22*	² 107,0±10,57**
3b: MRTB+ AIT (n=30)	¹ 10,71±0,98	¹ 1,08±0,04	¹ 4,87±0,98	¹ 6,13±1,05	¹ 57,00±7,16
	² 8,33±0,87**	² 3,87±0,67* **	² 4,24±0,96	² 7,58±1,15	² 76,50±11,54* **

Note 1: 1 - data before treatment; 2 - after 60 days of therapy.

Note 2: * The probable difference between the parameters within the group in the treatment ($p \leq 0.05$). . ** Likely difference between the indicators of observation and comparison groups ($p \leq 0.05$).

culosis and autoimmune thyroiditis a decreased average serum content of selenium (66.2 ± 8.30) $\mu\text{g} / \text{l}$ in group 1a and (66.36 ± 9.93) $\mu\text{g} / \text{l}$ in group 1b was noticed in compare with normal rate (4-130 $\mu\text{g} / \text{l}$ iter). Low-normal mean free thyroxine value (11.12 ± 0.8) pmol / l in group 1a and (11.21 ± 0.67) in group 1b and increase in TSH level (4.30 ± 1.20) $\mu\text{M} / \text{ml}$ in group 1a and (4.00 ± 1.41) $\mu\text{M} / \text{ml}$ in group 1b (Table 1) indicate the development of subclinical hypothyroidism in these patients.

Increase of antithyroid antibodies to thyroperoxidase to (42.64 ± 2.7) IU / ml in group 1a and to (38.54 ± 1.27) IU / ml in group 1b and thyroglobulin to (16.88 ± 1.39) IU / ml in group 1a and up to (18.54 ± 1.83) IU / ml in group 1b is a marker of the autoimmune process in the thyroid gland in patients with both subgroups (1a and 1b).

At the end of the intensive phase of chemotherapy, after a 2-month application of sodium selenite, the average level of selenium is likely to increase to (95.39 ± 8.45) $\mu\text{g} / \text{l}$ in group 1a compared with group 1b (68.50 ± 5.35) $\mu\text{g} / \text{l}$.

The level of free thyroxine in the group of patients 1a significantly increased to (13.32 ± 0.78) pmol / l , and the average level of TSH significantly decreased to (2.12 ± 0.90) IU / ml compared with

the control group (group 1b), in which on the background of chemotherapy there is a further decrease in the mean free thyroxine level to (8.12 ± 0.80) pmol / l and an increase in the average level of TSH to (4.80 ± 1.52) IU / ml compared with baseline levels these hormones. The level of anti-TPO antibodies is believed to decrease as compared with baseline levels (42.64 ± 2.72) IU / ml to (4.30 ± 0.14) IU / ml and compared with the comparison group (38.54 ± 1.27) IU / ml and (43.22 ± 1.65) IU / ml (Table 1). The level of antibodies to TG also decreases as compared with the starting level of (16.88 ± 1.39) IU / ml to (16.88 ± 1.39) IU / ml , and when compared with the comparison group in which the level Antibodies to thyroglobulin increase in the process of chemotherapy with ($18,54 \pm 1,83$) IU / ml to ($21,54 \pm 1,18$) IU / ml (Table 1). The results indicate the restoration of the function of the thyroid gland under the influence of selenium in patients with tuberculosis, as well as the tread effect of this trace element in the process of chemotherapy in the thyroid gland.

Autoimmune changes in the thyroid gland in co-infection with TB / HIV are accompanied by selenium deficiency 63.27 ± 10.79) $\mu\text{g} / \text{l}$ (group 2a) and (64.01 ± 9.43) $\mu\text{g} / \text{l}$ (group 2b). The prescription of sodium selenite restores selenium to normal (94.69

Table 2

Results of chemotherapy in patients with tuberculosis and autoimmune thyroiditis, depending on the level of selenium

Parameters	TB+AIT+Se (n=30) Abs. (%)	TB+AIT (n=30) Abs. (%)	TB/HIV+ AIT+Se (n=30) Abs. (%)	TB/HIV+ AIT +Se (n=30) Abs. (%)	MRTB+ AIT+Se (n=30) Abs. (%)	MRTB+ AIT (n=30) Abs. (%)
Stopping of bacilli excretion	24 (80)	26 (86,66)	20 (66,66)	14 (46,66)	15 (50,0)	17 (56,66)
Cavities healing	15 (50)	11 (40,0)	13 (43,33)	10 (33,33)	10 (33,33)	7 (23,33)

µg / l). This group of patients also has a decrease in its hormonal activity, as evidenced by the average low-normal value of the level of free thyroxine (9.89 pmol / l) and a fairly high level of TTG (3.43 IU / ml). In the comparison group (group 2b), chemotherapy in the intensive phase leads to an increase in the average level of TSH (from 3.43 to 4.12 IU / ml), which indicates a weakening of the thyroid status of a patient with co-infection with tuberculosis / HIV under the influence of anti-TB drugs. The application of sodium selenite in the observation group of patients with co-infection leads to a significant increase in the mean free thyroxine level within the normal range (12.97 pmol / l) and a decrease in TSH level to normal (1.87 µM / ml), which optimizes the functional state thyroid gland without the use of thyroid hormones. In the group of co-infected patients receiving sodium selenite, there is also a significant decrease in the average level of antibodies to thyroperoxidase as compared to the baseline (from 31.12 to 2.12 IU / ml) and in comparison with the comparison group (2.12 and 6.77 IU / ml).

In the group of patients with multidrug-resistant tuberculosis and with pathological changes of the thyroid gland, the lowest average selenium level is observed in comparison with other groups (56.66 µg / l) (group 3a) before treatment commences. In the same group, there is a low-normal mean free thyroxine level (10.22 pmol / l) with normal values of TSH (1.08 IU / ml). In the comparison group (group 3b), on the background of intensive chemotherapy, a decrease in the mean free thyroxin level to a low anomalous value (from 10.71 to 8.33 pmol / l) was recorded.

The application of sodium selenite in the observation group 3a, restoring the normal content of selenium in the blood to 107.0 µg / l, not only prevents further reduction of free thyroxine, as in the comparison group 3b, but also causes its significant increase within normal physiological values (14, 34 pmol / liter).

The results of the study show the damaging effect of tuberculous infection on the thyroid gland and the presence of subclinical hypothyroidism in patients

with tuberculosis with structural thyroid disorders. The obtained data confirm the ability of anti-TB drugs to reduce the function of the thyroid gland, as noted by numerous studies.

Sodium selenite, compensating for the deficiency of selenium in the body of patients with tuberculosis and autoimmune thyroiditis, restores the function of the thyroid gland in the observation groups (*groups 1a, 2a and 3a*), while in the comparison groups (*groups 1b, 2b and 3b*) in the process phase of intensive chemotherapy there is a further weakening of the thyroid function. The results of the study also confirm the ability of selenium to lower the titer of antibodies to thyroperoxidase, as reflected in a number of publications [14, 19, 24].

Thus, selenite sodium provides a tread and stimulating effect on the thyroid gland of patients with tuberculosis with autoimmune thyroiditis and subclinical hypothyroidism or pathological euthyroid syndrome and may be recommended as a therapy for the maintenance of chemotherapy in these individuals.

In evaluating the effect of selenium on the results of chemotherapy of patients with tuberculosis until the end of the intensive care phase, it was found that in 1a, the bacterial excretion stopped in 24% of patients, which is 6.66% more than in the comparison group. In the same group, the rate of healing of caverns is 10% higher when compared with the control group (*group 1b*) (Table 2).

In the group of TB / HIV co-infected patients receiving selenium (*group 2a*), stopping of bacilli excretion to the end of the intensive care phase occurred in 20 cases (66.66%), in the comparison group - in 14 cases (46.66%) (*group 2b*). The destruction of destructions in this group came in 13 (43,33%) - by 10% more compared with the comparison group - 10 cases (33,33%). In patients with multi-resistant tuberculosis with pathology of the thyroid gland receiving sodium selenite, stopping of bacilli excretion to the end of the intensive care phase occurred in 15 cases (50.0%) and the destruction of lesions - in 10 cases (33.33%). The

corresponding indicators in the comparison group were 17 cases (56.66%) 7 cases (23.33%).

The obtained results reflect the positive effect of selenium on the results of chemotherapy, increasing the termination of bacterial release by 6.66% - 20% and healing destruction by 10% when compared with control. The obtained data confirm the results of studies by other authors on the positive effects of selenium on the effects of TB treatment [15].

Conclusions

1. In patients with tuberculosis and AIT in a drug-susceptible process and co-infection with tuberculosis / HIV, subclinical hypothyroidism is observed, and in the case of multi-resistant tuberculosis, a pathological euthyroid syndrome.

2. Anti-tuberculous chemotherapy, which includes rifampicin, thioamides and PAS in patients with tuberculosis and AIT leads to further deepening of hypothyroidism.

3. Inclusion in the complex therapy of various groups of patients with tuberculosis in combination with AIT of sodium selenite leads to the restoration of the function of the thyroid gland and provides a tread effect in relation to thyrotoxic action of anti-TB chemotherapeutic agents.

4. The appointment of sodium selenite in the intensive phase of treatment of patients with tuberculosis in combination with AIT improves the results of chemotherapy, which leads to an increase in stopping of bacilli excretion by 6.66% -20% and healing destruction by 10% when compared with control.

5. Sodium selenite may be recommended as a satellite therapy when performing chemotherapy of a patient with tuberculosis and AIT in combination with subclinical hypothyroidism and pathological euthyroid syndrome.

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ПРОФИЛАКТИКА РЕЦИДИВОВ МУЛЬТИРЕЗИСТЕНТНОГО ТУБЕРКУЛЕЗА С ИСПОЛЬЗОВАНИЕМ ИННОВАЦИОННЫХ ТЕХНОЛОГИЙ

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Резюме

Высокий удельный вес широкой мультирезистентности микобактерий туберкулеза среди новых случаев заболевания туберкулезом, рост частоты выявления запущенных деструктивных форм мультирезистентного туберкулеза (МР ТБ) с наличием поликаверноза среди впервые диагностированных случаев обуславливает поиск новых, пациент-ориентированных подходов к ведению случая. Назначение индивидуальных режимов этиопатогенетического лечения с применением средств разнонаправленного действия - озон-лазеротерапии позволяет повысить результативность химиотерапии, увеличить частоту «излечения» больных, предотвращает развитие рецидива МР ТБ легких.

Ключевые слова: профилактика, рецидив, мультирезистентный туберкулез

Summary. Prevention of multidrug-resistant tuberculosis reactivity with using innovation technologies

The high proportion of advanced and pre-expanded multidrug resistance TB mycobacteria in both new and repeated cases of tuberculosis, an increase in the frequency of detection of neglected destructive forms of multidrug-resistant tuberculosis (MR TB) with the presence of polycavernosis among the newly diagnosed cases leads to the search for new, patient-oriented approaches to case management. The appointment of individual regimens of etiopathogenetic treatment with the use of means of multi-directional action - ozone laser therapy can increase the effectiveness of chemotherapy, increase the frequency of «cure» of patients, which prevents the recurrence of MR TB.

Key-words: prevention, relapse, multidrug-resistant tuberculosis

Туберкулез продолжает оставаться глобальной проблемой во всем мире, в том числе и в Украине, хотя в последние годы отмечается стабильная положительная динамика в снижении эпидемических показателей (заболеваемости и смертности), однако снижения удельного веса лекарственно-устойчивого туберкулеза легких остается недостаточным, что приводит к увеличению количества больных мультирезистентным туберкулезом (МР ТБ), которые пополняют контингенты противотуберкулезных диспансеров больными с рецидивом

МР ТБ. Регистрируемый рост удельного веса как среди впервые выявленных больных МР ТБ (21,4%), так и больных с рецидивом заболевания (45,8%) свидетельствует не только о повышении эффективности лабораторных технологий выявления лекарственной устойчивости микобактерий туберкулеза (МБТ), но и формирования «резервуара мультирезистентной инфекции». Наиболее неблагоприятными в эпидемиологическом и клиническом отношении являются больные с множественной лекарственной устойчивостью МБТ, что