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The efficacy of treatment and prophylaxis in allergic complications of pulmonary tuberculosis

Key words: tuberculosis, immune system and oxidant-antioxidant system, side effects of drugs, prevention and treatment of adverse reactions.

Over the last 10–15 years, the epidemic situation with tuberculosis remains tense. [11] Aetiotropic therapy is still one of the main factors against this infectious disease [12]. Drug therapy allowed achieving significant success in the treatment of this specific process. However, antibacterial therapy of tuberculosis may be complicated by adverse reactions to specific treatment modalities [4, 7]. One of the most dangerous complications of drug therapy is drug allergy [10].

With years, the problem of adverse action of drug progressively gains relevance, which is related both to deteriorating environment adversely affecting human body and to increasing numbers of tuberculosis patients with comorbidities, the types of chemotherapy used, etc. [5, 16, 17]. The efficacy of drug therapy for tuberculosis is adversely affected by advanced pulmonary tuberculosis, poor compliance in certain patient populations, etc. [3].

A substantial number of scientific reports was focused on complications of drug therapy; however, multiple issues concerning their origin and progress are still far from their final clarification [6, 8]. Immune system and oxidant-antioxidant processes play an important role in the origin and progress of adverse reactions to drugs; therefore, immune and oxidant-antioxidant studies are of unquestionable theoretical and applied value [14].

There is a pending challenge to create the system of measures and approaches to facilitate prevention and treatment of drug complications different clinical forms and extent of tubercular process, duration of disease, allergic and pharmacotherapeutic history, comorbidities, therapies and other characteristics.

The chronic conditions concomitant to pulmonary tuberculosis (PTB) play a negative role in tolerability of anti-mycobacterial drugs [16]. An important objective of tuberculosis science (Phthisiology) is minimizing the influence of comorbidities on efficacy of PTB drug therapy and tolerability of antibacterial drugs.

Immune correction therapy is widely used by tuberculosis specialists to increase the efficacy of tuberculosis treatment [1]. However, allergic reactions to anti-mycobacterial drugs such therapy frequently deteriorates the tolerability of the latter [2], which necessitates further studies of this problem.

Plasmapheresis (PP) is one of the methods with radical influence on human body with an important role in the treatment of many diseases [15]. There are but isolated reports on using plasmapheresis in tuberculosis [13]; however, there are no reports concerning using this method to eliminate and prevent adverse reactions to anti-tuberculosis drugs (ATD).

The relevance of the chosen research topic is determined by the studies of immune aspects of PTB pathogenesis, non-complicated drug therapy and adverse allergic reactions to TB-specific drugs, determination of optimized methods to eliminate and prevent these complications, employing measures to improve ATD tolerability and the need to increase the efficacy of tuberculosis treatment in the light of adverse reactions to TB-specific drugs.

Study objective: To increase the efficacy of treatment for pulmonary tuberculosis and allergic reactions to anti-tuberculosis drugs. To substantiate and design the system of measures to prevent and eliminate the allergic complications of drug therapy.

Materials and methods

In accordance with the assigned tasks, the patients were divided into the following groups:

Group I (148 subjects) consisted of patients with onerous allergy and pharmacological history (AAH) and latent allergy to ATDs.

Group II (358 subjects) consisted of patients with clinical manifestations of adverse allergic reactions to TB-specific drugs, which were subject to different methods to prevent and eliminate these complications.

Group III (control group) consisted of patients without adverse reactions to ATDs (178 subjects).

Analysis of medical records was performed in 281 patients receiving in-patient fundamental drug therapy (mostly 43 ATDs, then 3 ATDs) to define the frequency and patterns of adverse reactions to antibacterial drugs. Adverse reactions to ATDs were documented in 193 subjects ($68,7 \pm 2,8$ %) (Table).

Allergic complications were seen in 71 patients – ($25,3 \pm 2,6$ %). The proportion of allergic complications to all complications was 36.8 %. If purely allergic complications are pooled with toxic-allergic complications, the overall incidence of allergic complications of DT is ($38,1 \pm 2,9$ %) (107 patients) and the proportion of allergic complications to all complications is 55.4 %.

Adverse allergic reactions to anti-tuberculosis drugs were almost 2.3 times more common ($p < 0.001$) in focal disseminated pulmonary tuberculosis, FDPTB ($29,8 \pm 3,2$ %) than in drug-resistant pulmonary tuberculosis, DRPTB ($13,2 \pm 3,9$ %); toxic reactions – were 1.4 times less frequent – ($27,8 \pm 3,1$ %) and ($38,2 \pm 5,6$ %), respectively ($p > 0.05$).

History findings play an important role in ATD tolerability. It was found that in 82 patients with PTB and onerous AAH adverse reactions to TB-specific drugs had occurred in 64 ($78,0 \pm 4,6$ %) cases, whereas the respective incidence – in 129 of 199 cases ($64,8 \pm 3,4$ %) uncomplicated history ($p < 0.05$). No significant differences in terms of adverse reactions to ATDs were found between urban and rural residents; neither were drug-related adverse events (AEs) dependent on patient's blood type. The incidence of AEs is substantially influenced by the ability of the body to deactivate certain ATDs. Inactivation of isoniazid was studied in 162 PTB

patients. In slow isoniazid acetylators, complications of ATDs were documented in 96 of 135 patients ($71,1 \pm 3,9$ %), whereas in slow acetylators such complications were found – in 15 of 27 patients or ($55,6 \pm 9,6$ %) ($p > 0.05$).

Adverse allergic reactions to TB-specific drugs are three times more frequent in the summer (in 33 patients ($17,1 \pm 2,7$ %)), than in winter (in 11 patients ($5,7 \pm 1,7$ %), $p < 0.001$). The complications of toxic origin were uniformly distributed throughout the year, with a certain predominance in the autumn-winter period (autumn-winter – in 51 patients ($26,4 \pm 3,2$ %), spring-summer – in 35 ($18,1 \pm 2,8$ %), $p > 0.05$). Adverse allergic reactions to ATDs were more frequent hyperergic reaction to 2TU of PPD-L – in 7 of 12 ($58,3 \pm 14,2$ %) compared to hypoergic reactions – in 6 of 25 – ($24,0 \pm 8,5$ %) and with normoergic reactions – in 53 of 222 ($23,9 \pm 2,9$ %), $p < 0.05$).

Conditions concomitant to PTB were observed in 141 ($50,2 \pm 3,0$ %) patients; more than a third of these patients had two and more comorbidities. Adverse reactions to ATD had occurred in 105 ($74,5 \pm 3,7$ %) patients with concomitant disease.

Adverse reactions to TB-specific drugs significantly hamper healing of destruction foci in the lungs. Thus, after 3 months of non-complicated DT the caverns healed in ($46,9 \pm 8,8$ %) patients and in ($26,9 \pm 4,6$ %) patients ($p < 0.05$) with AEs related to TB-specific drugs. After 8 months – ($96,9 \pm 3,2$ %) and ($87,1 \pm 3,5$ %), respectively ($p < 0.05$). Slow healing of caverns in ATD-related complications leads to a longer in-hospital treatment of the patients. In non-complicated DT average hospital stay was ($164,4 \pm 8,0$) days; in complicated DT average hospital stay – ($203,3 \pm 5,8$) days ($p < 0.001$), which is 39 days longer.

An important role in prevention of DT-related allergic complications is played by AAH; meticulous AAH study gives grounds to divide all patients into subjects with onerous and uncomplicated history.

Since drug allergy to ATD is more frequent in PTB patients with onerous AAH, DT in these patients was carried out at the background of non-specific hyposensitization (NSHS), the latter characterized by substantial duration. The technique involves the use of NSHS for not less than two months from the first days of PTB treatment. The schedules of long-term

The pattern of complications of anti-tuberculosis drug therapy in patients with pulmonary tuberculosis

Table

The type of tuberculosis The pattern of adverse reactions	FDPTB (n = 205)		DRPTB (n = 76)		Conclusion: (n = 281)	
	Abs.	Relat., %	Abs.	Relat., %	Abs.	Relat., %
Toxic	57	$27,8 \pm 3,1$	29	$38,2 \pm 5,6$	86	$30,6 \pm 2,7$
Allergic	61	$29,8 \pm 3,2^*$	10	$13,2 \pm 3,9^*$	71	$25,3 \pm 2,6$
Mixed	27	$13,2 \pm 2,4$	9	$11,8 \pm 3,7$	36	$12,8 \pm 2,0$
Total	145	$70,7 \pm 3,2$	48	$63,2 \pm 5,5$	193	$68,7 \pm 2,8$

Note: * – the difference between the findings of FDPTB and DRPTB is significant ($p < 0.001$).

non-specific hyposensitization (LTNSHS) included glucocorticoids, antihistamines, calcium, sodium thiosulphate, Presocyl, Askorutin, etc. The latter schedules include changing the above drugs every two weeks (with the exception of glucocorticoids received by the patients over one month at 20 mg of prednisolone per day every other day).

The technique was used in 148 PTB patients with onerous allergy and pharmacotherapy history and latent allergy to ATD, which was detected by in vitro testing (specific drug-positive leukocyte agglomeration reactions and leukocyte migration inhibition tests).

There were 116 patients with onerous history. The LTNSHS schedules were used in 49 of these patients. No such hyposensitization was employed in other patients. ATD-related allergic adverse events have occurred at the background of LTNSHS in 19 of 49 patients - $(38,8 \pm 6,9) \%$. The above technique was not employed in 56 of 67 patients - $(83,6 \pm 4,5) \%$ ($p < 0.001$).

Thirty-two patients with latent allergy to ATDs were treated. LTNSHS was performed in 20 of these patients. This technique has proven effective in 16 (80.0 %) patients; lack of efficacy was found - in 4 patients (20.0 %). The remaining patients (which did not have NSHS) had ATD-related allergic complications in course of DT in 7 of 12 cases (58.3 %). The data indicate a high efficiency of LTNSHS in patients with latent allergy to ATDs. The differences across the groups were significant (χ -square was 10.06; $p < 0.001$).

Moderate and pronounced adverse allergic reactions to ATDs during peaks of complications were relieved within 10-14 days by administration of desensitizing agents (chiefly parenteral). The following agents were used 30% solution sodium thiosulphate, 1% solution of calcium chloride, glucocorticosteroid hormones and antihistamines. The results of using LTNSHS are given below.

In 358 PTB patients with drug-induced ATD-related complications of allergic and toxic-allergic patterns, adverse reactions were manifest as rash or eosinophilia (both as independent symptoms and in combinations with other manifestations, such as drug-induced hepatitis, problems with central and peripheral nervous system, hyperthermia, etc.). Seven patients had drug-induced anaphylaxis. These patients were subject to measures aimed at relieving clinically manifest complications, such as discontinuation of ATDs and non-specific hyposensitization.

Such a radical approach to drug allergy as drug discontinuation does not always safeguard the patient from AEs recurrence. Discontinuation of the drug in 32 PTB patients with allergic ATD-related complications produced a positive effect in 26 (81.2 %) patients. In 6 (18.8 %) cases discontinuation of the drug resulted in clinical elimination of AEs, but allergic complications re-emerged with subsequent treatment. Therefore, the patients that experienced DT complications of allergic origin should have their NSHS continued. LTNSHS should become the method of choice.

The efficacy of long-term and shortened NSHS is presented at the example of 266 PTB patients with allergic reactions to ATDs. LTNSHS was performed in 177 patients; the shortened procedure was performed - in 89. Whereas in LTNSHS the recurrences of drug-related complications were $(20,9 \pm$

$3,0) \%$, then in shortened procedure the recurrences were seen in $(58,4 \pm 5,2) \%$ cases ($p < 0.001$). It is important to note that the patients receiving long-term NSHS were able to resume their previous DT schedules in $(57,8 \pm 4,2) \%$ cases; in shortened NSHS this was possible - in $(32,4 \pm 2,7) \%$ cases ($p < 0.01$).

Taking into consideration the limited options of selecting highly effective ATDs, there was repeated use of the latter (with improved tolerability) covered by the technique of specific hyposensitization (SHS). SHS was performed after clinical manifestations of drug allergy were completely eliminated against the background of NSHS followed by LTNSHS. Specific hyposensitization was performed in 60 patients with different complications of allergic and toxic-allergic origin. Positive effect, that is, ensuring a favourable tolerability of ATDs, which previously caused pronounced allergy, was achieved in 41 patients (68.3 %).

The greatest efficacy was achieved with LTNSHS schedules containing glucocorticosteroid hormones, sodium thiosulphate, Presocyl, injectable calcium and antihistamines. Thus, combinations with prednisolone were effective in 83.3 % cases, combinations with Presocyl were effective - in 80.0 % cases and combinations with sodium thiosulphate and antihistamines were effective - in 79.3 % cases.

Pronounced adverse reactions to ATDs, recurrent complications of DT and AEs in combination with comorbidities and marked toxemia called for more decisive methods of therapeutic impact on body systems. Plasmapheresis (PP) proved an effective technique in that regards; the procedure was performed in 138 patients. PTB was disseminated. General condition was severe or moderate in 68 subjects; 66 patients had conditions concomitant to PTB. Drug-related complications were persistent and occasionally recurrent. Each patient had 3 to 5 sessions of plasmapheresis. Full clinical effect of PP was achieved in 122 (88.4 %) patients; partial clinical effect was achieved - in 13 (9.4 %) patients. No effect was seen in three (3) subjects (2.2 %). Clinical manifestations of AEs began to resolve already after two sessions if PP in 78 (56.5 %) patients; in 54 more patients (39.1 %) these manifestations resolved after three sessions and in 3 more patients (2.2 %) these manifestations resolved after four sessions.

The influence of immunomodulators and immunocorrectors on both efficacy of measures to eliminate AEs and DT efficacy was studied in 112 PTB patients.

The measures to eliminate AEs were effective only in 45 of 112 patients $(40,2 \pm 4,6) \%$, which received immune correction agents along with ATDs. The best results were obtained in administration of Splenin - $(55,6 \pm 8,3) \%$, the results of using sodium nucleinate were inferior - $(42,8 \pm 8,4) \%$; substantially worse results were observed with levamisole - $(24,4 \pm 6,7) \%$. The frequency of AE elimination was significantly higher in PTB patients with AEs, who received no immune correction - $(73,8 \pm 3,9) \%$ in 93 patients of 126 ($p < 0.01$).

There is a notable difference in terms of DT efficacy between these two groups and the patients without AEs. In PTB patients with AEs receiving immune correction therapy and hyposensitizing agents (Group I), in two months of DT 56 of 93 patients - $(60,2 \pm 5,1) \%$ had sputum conversion.

Patients with AEs to ATDs and hyposensitization (but without immune correction (Group II) had substantially higher values - 74 of 91 patients - ($81,3 \pm 4,1$) % ($p < 0.002$). The above values were higher in PTB patients without AEs and with corrective therapy (Group III), that is ($91,2 \pm 3,4$) % or 63 of 69 subjects, which was a higher value than in the patients of Group I ($p < 0.001$) and Group II ($p > 0.05$). The overall incidence of sputum conversion was almost uniformly high in all groups: Group I - ($91,4 \pm 2,9$) %, Group II - ($94,5 \pm 2,4$) % and Group III - ($98,6 \pm 1,6$) % with an insignificant trend towards greater values in Group II and Group III ($p > 0.05$).

The situation is seen more clearly, when the parameters of cavern closure are compared. In five months of DT pulmonary cavities have healed in ($28,3 \pm 4,5$) % cases (28 of 99 patients) in Group I; in ($48,5 \pm 5,0$) % cases (48 of 99 subjects) in Group II, $p < 0.01$) and in ($86,8 \pm 3,9$) % cases (66 of 76 patients) in Group III. The latter figure was significantly higher than in the first and the second group ($p < 0.001$). At discharge, the outcomes concerning cavern healing were almost identical in the first two groups - ($77,8 \pm 4,2$) % and ($81,8 \pm 3,9$) %; however, these results were significantly lower ($p < 0.001$) than the results in the patients of Group III - ($98,7 \pm 1,3$) %.

The tolerability of DT is significantly affected by the conditions concomitant to PTB, especially the conditions of gastrointestinal tract and the liver. We have observed 114 PTB patients with AEs. Fifty-three patients with tuberculosis had peptic ulcer in remission; 61 patients had liver disease (hepatitis, cholecystitis). The population of 190 subjects without any of the above comorbidities served as controls. It was estimated that disseminated pulmonary lesions in patients with concomitant peptic ulcer were found in ($43,4 \pm 6,8$) % cases; these lesions were seen in liver disease in ($31,2 \pm 5,9$) % cases ($p > 0.05$) and in ($27,4 \pm 3,2$) % subjects ($p < 0.05$) without obvious disease.

The probability of peptic ulcer exacerbation depended on approaches to this patient population. The patients receiving anti-ulcer drugs prior to and during DT had exacerbation of peptic ulcer in 1 of 13 patients; the patients without any anti-ulcer preventive treatment had a different ratio - 24 of 40 patients. The inter-group differences are significant ($p < 0.001$). Exacerbation of peptic ulcer had negative impacts on both efficacy of counter-AE interventions and the efficacy of DT. The efficacy of counter-AE interventions was ($41,5 \pm 6,8$) % (22 of 53 patients); sputum conversion was achieved in 26 of 31 patients ($83,9 \pm 6,6$) % and closure of decay cavities was achieved in 17 of 41 patients ($41,5 \pm 7,7$) %.

A similar picture was observed in regards to DT in PTB patients with concomitant liver disease. Among the patients receiving hepatoprotectors during DT, exacerbation of hepatic process had occurred in 1 of 16 patients; concerning patients who did not receive hepatoprotectors, such complications were observed in 38 of 45 patients ($p < 0.001$). In patients with liver disease, AE elimination was possible - in ($42,6 \pm 6,3$) % patients (26 of 61 patients), sputum conversion was achieved - in ($81,4 \pm 5,9$) % (in 35 of 43 patients) and closure of pulmonary decay cavities was seen - in ($71,1 \pm 6,8$) % patients (32 of 45 patients).

Regarding patients without comorbidities, AE elimination was effective in ($75,8 \pm 3,1$) % patients (in 144 of 190 patients), sputum conversion was achieved in ($97,7 \pm 1,3$) % (in 129 of 132 patients) and closure of destruction foci was documented in ($82,5 \pm 2,9$) % patients (in 137 of 166 patients). The figures in the last group were significantly higher than in the first two ($p < 0.05$).

Therefore, the negative impact of AEs is increased whenever patients have conditions concomitant to PTB, especially those of digestive system and the liver, which requires appropriate pharmacological therapy for such alterations.

Whenever DT is undertaken in patients with onerous AAH / allergic complications of ATDs, a special approach is required, as well as a system of interventions for allergic complications and their prevention. We believe that starting with the first days of DT, the patients with onerous AAH history should receive long-term non-specific hyposensitization along with their ATDs. The same approach should be employed in management of PTB in patients with occult ATD sensitization. Patients with drug allergy at the background of DT must receive NSHS after discontinuance of the drugs (not only until the clinical manifestations of AEs are resolved, but further as well). Therefore, any further DT should be covered with at least 2 months of NSHS. The intensity and duration of hyposensitization is determined by the severity of drug allergy. NSHS methods also include discrete plasmapheresis, which produces short-term positive effects in patients with drug-induced complications. This method is quite effective not only as a preventive intervention (which is of particular significance in patients with allergic disease and pronounced tuberculosis toxemia) but also as a therapeutic measure which greatly improves ATD tolerability and decreases the intensity of respective adverse reactions.

Conclusions

1. Adverse reactions to ATDs in patients with pulmonary tuberculosis occur significantly more frequently in onerous allergy and pharmacotherapy history, in slow isoniazid inactivation, in patients with hyperergic tuberculin tests and mainly gastrointestinal and hepatic comorbidities. The incidence of complications remains consistently high during the last 20–25 years.

2. Adverse reactions to ATDs substantially slow down healing of pulmonary destructive lesions and (to a lesser degree) affect sputum conversion compared to complication-free patients; the outcome of sputum conversion is virtually identical ($94,5 \pm 2,0$) % and ($95,0 \pm 3,4$) %, respectively). There is a somewhat lower outcome of cavern healing - ($87,1 \pm 3,5$) % and ($96,9 \pm 3,2$) %, respectively, ($p < 0.05$). Delays of destruction lesion healing prolongs hospital stay by 23.8 % in patients with adverse effects of drugs.

3. Long-term non-specific hyposensitization (LTNSHS) substantially reduces the risks of drug allergy to ATDs in patients with pulmonary tuberculosis with onerous allergy and pharmacotherapy history (from ($83,6 \pm 4,5$) % to ($38,8 \pm 6,9$) % ($p < 0.001$) and latent allergy to TB-specific drugs. LTNSHS promotes a faster elimination of ATD-triggered allergic complications and a substantial decrease in recurrences of the latter when chemotherapy is resumed. Return

to prior schemes of DT after LTNSHS is possible - in (57,8 ± 4,2) % patients; in shortened NSHS this was possible only in (32,4 ± 2,7) % patients ($p < 0.01$).

4. An effective method to retain effective (but allergy-triggering) ATDs within chemotherapy schedules is specific hyposensitization in combination with LTNSHS. Using this method allowed achieving a positive effect in 68.3 % patients.

5. Discrete plasmapheresis is a highly effective and readily available technique to eliminate severe allergic reactions to ATDs, to manage recurring complications of drug therapy, as well as complications combined with comorbidities and pronounced toxemia; the technique allows eliminating clinically manifest complications in 97.8 % patients, with 56.7% patients achieving such results with as few as two sessions.

6. The efficacy of LTNSHS in allergic and toxic-allergic complications of anti-tuberculosis therapy is significantly decreased in administration of immune correcting agents (Splenin, sodium nucleinate and levamisole), as well as the efficacy of drug therapy in this patient population.

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ЭФФЕКТИВНОСТЬ ЛЕЧЕНИЯ И ПРОФИЛАКТИКА АЛЛЕРГИЧЕСКИХ ОСЛОЖНЕНИЙ У БОЛЬНЫХ ТУБЕРКУЛЕЗОМ ЛЕГКИХ

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Резюме. На основе клинических наблюдений за 684 больными туберкулезом легких (ТБЛ) уточнены некоторые вопросы патогенеза медикаментозной аллергии — определено состояние иммунной системы у больных ТБЛ без аллергических осложнений, возникающих при применении специфических средств, и с аллергическими побочными реакциями к ним. Впервые разработана и обоснована система мероприятий по профилактике и устранению медикаментозной аллергии на противотуберкулезные препараты различных групп больных ТБЛ (длительная неспецифическая гипосенсибилизация, специфическая гипосенсибилизация в комбинации с длительной неспецифической, дискретный плазмаферез в комбинации с длительной неспецифической гипосенсибилизацией). Впервые определены новые подходы к использованию иммунокорригирующих средств у больных ТБЛ на фоне медикаментозной аллергии. Предложены подходы к химиотерапии больных ТБЛ с сопутствующей язвенной болезнью желудка и двенадцатиперстной кишки и патологией печени.

Ключевые слова: туберкулез, иммунная система, побочное действие лекарств, профилактика и лечение побочных реакций.

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THE EFFECTIVENESS OF THE TREATMENT AND PREVENTION OF ALLERGIC COMPLICATIONS IN PATIENTS WITH PULMONARY TUBERCULOSIS

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Summary. Observations of 684 patients with pulmonary tuberculosis (PTB) are based on specifying some problems of medicinal allergy pathogenesis — there has been determined the state of immune system in PTB patients with good tolerance of specific drugs and with their allergic side-effects. For the first time there has been elaborated and grounded the system of measurements as for the prophylaxy and elimination of medicinal allergy to antituberculous preparations of different groups of PTB patients (prolonged non-specific hyposensitivity, specific hyposensitivity combined with prolonged non-specific hyposensitivity, discrete plasmapheresis combined with prolonged non-specific hyposensitivity). For the first time there have been determined new approaches to using immunocorrective drugs in PTB patients with medicinal allergy. There have been also suggested approaches to chemotherapy of PTB patients with concomitant gastric and duodenal ulcer and liver pathology.

Key words: tuberculosis, immune system, side-effects of drugs, prophylaxy and treatment of side-effects.

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