N.F. Bilib [1969], based on measuring separate and total blood bacteriostatic activity 3 and 6 hours after administering isoniazid, PAS and streptomycin, established an increase in blood bacteriostatic activity (BBA), due to their synergic effect on mycobacteria, as well as due to preventing INH inactivation.

T.I. Kozulatsyna and G.A. Korotayev [1969], when combining oral administration of isoniazid and PAS, discovered that blood concentration of active INH is increased, on average, 2.6 times compared to oral administration of isoniazid alone.

H. Titinen [1969] demonstrated that administration of isoniazid together with PAS increases INH half-life both in quick and slow inactivators.

Particularly high blood and tissue PAS concentration in tuberculosis patients was observed after intradrop administration of the daily dose of the drug. According to the data of K. Paul [1960], the tissue concentration of the drug in such cases reached as high as 500 µg/g, while lung and kidney concentration was even higher. He established that at 120 µg/g blood PAS concentration, the liver acetylates only 20% of the drug, and believed that the intravenous drug administration is the best method to prevent side effects.

E. Deberschauer [1963] emphasized that intravenous administration of 500 ml 4.8% PAS solution during 2.5 hours allows maintaining high concentration of the drug (up to 200-250 µg/ml) for 12 to 14 days. Administration of the same dose PAS orally leads to blood serum concentrations of 66 µ/ml and less, which is 3 to 4 times lower in comparison.

N.Y. Batmanov, Y.G. Grygoriev and S.S. Kanaveskaya [1971] reported that total bacteriostatic blood activity achieved with intravenous drop administration of streptomycin, isoniazid and PAS is 4.5 times higher compared to that of the traditional administration method. It is one of the most active chemotherapy methods, since cavity closure is observed in 76% patients with fresh tuberculosis forms in the first 4 to 6 months.

According to the data of N.N. Kovalenko, drug concentration in resected lung of tuberculosis patient 1.5-2 hours after per os administration of 12 g PAS was 29 µg/g, on average, while after intravenous administration of the same dose, the drug concentration was incongruously higher both in the cavern wall and the focus – 230 µg/g. Therefore, intravenous administration increases the likelihood of bactericidal effect.


Seeing as intravenous administration of tuberculostatic drugs proved to be much more effective than intramuscular administration of streptomycin concurrent with oral isoniazid and PAS, such 3-4 month courses of intravenous drop therapy have destined the field of research and practice of tuberculosis treatment facilities of our country [Koronenko, 1964; Grygoriev, Kanaveskaya, 1966; Repin, 1966; Pilipchuk, Kolesnikova, 1967; Shebanov, Grygoriev, 1967; Punga et al, 1968; Rudoy, Utkin, 1969; Voinova, Badreddinov, 1970; Pilipchuk et al, 1970; Gerasimenko et al, 1973].

Intravenous drop chemotherapy was mainly prescribed in patients with open and cavernous forms of pulmonary tuberculosis, after the combination of oral isoniazid and PASA, and intramuscular streptomycin proved ineffective, or in preparation for surgery.

H. Herzog et al [1960] achieved cavity closure after 4 months in 48% of 170 patients with newly-diagnosed destructive tuberculosis treated by intravenous administration of isoniazid, PAS and streptomycin-pantothenate for 5 to 15 weeks, followed by traditional therapy.

According to the data of E. Kuntz [1959], 3 to 5 months of intravenous therapy with streptomycin-pantothenate, isoniazid and PAS, abacillation was observed in 62% of pulmonary tuberculosis patients, while cavity closure was achieved in 42% patients.

As indicated by L.P. Stambolytsyn, cavity closure was observed after 1.5 to 4.5 months in 58.5% of 108 Algerian patients with pulmonary tuberculosis treated with intravenous streptomycin, isoniazid and PAS. This result achieved within 3 months of treatment is considered highly satisfactory.

P.S. Murashkin and G.S. Murashkina of the Novosibirsk Research Institute for Tuberculosis, who had visited Algeria later, reported at the conference held at their institute, drawing the attention of their colleagues to the great effectiveness of intravenous streptomycin, isoniazid and PAS for treatment of widespread tuberculosis and caseous pneumonia, especially combined with supplemental therapy with nutritional formula to eliminate protein deprivation.

The first report on the effectiveness of intravenous streptomycin, isoniazid and PAS in patients with newly-diagnosed destructive pulmonary tuberculosis, administered ever other day (3 times weekly) without preliminary daily chemotherapy was delivered by N.I. Serebrova, V.G. Kononenko, L.N. Sharapova, M.I. Kiskevich and S.A. Savelova at the VIII Union Phthisiologist Congress in 1973. At the same time, the Novosibirsk Research Institute for Tuberculosis, over several years, has accumulated a volume of clinical experience indicating high effectiveness of intravenous chemotherapy with 1-2 day intervals (i.e. administered intermittently) for treatment of destructive tuberculosis in adults as well as for recovery of children and teenagers with aggravated pulmonary processes, received by the institute [Kononenko, 1974; Savelova et al, 1974; Sharapova et al, 1974]. Furthermore, a research was conducted, aimed at significantly decreasing the duration of artificial pneumothorax under conditions of intravenous administration of streptomycin, isoniazid and PAS thrice weekly, in patients with newly-diagnosed destructive pulmonary tuberculosis [Kuzina et al, 1974; Krupenko et al, 1974]. Some of these studies have become basis for successful doctoral candidate theses later.

N. Kurunov et al [1982] achieved experimental validation of intermittent intravenous chemotherapy of tuberculosis. They demonstrated that intravenous therapy administered 3 and 2 times weekly allows for practical creation of a scientific tuberculostatic focus in the lesion, but in contrast to standard regimens, the drug concentration in the lesion is significantly higher. Y. N. Kurunov et al [1976] observed 215 patients aged 18 to 59 with newly-diagnosed pulmonary tuberculosis in the decay phase or sputum smear-positive pulmonary tuberculosis. 60 of the patients received streptomycin, isoniazid and PAS daily, according to the traditional method (intramuscularly) and orally, while the rest received the same drugs by intravenous drop infusion, daily or intermittently. The patient groups were sufficiently representative in terms of clinical forms, sex, age and other parameters. 163 patients have been treated for 3 to 6 months, while the remaining 52 for 7 to 10 months.

Direct results of traditional chemotherapy were considerably worse compared to intravenous therapy: intoxication symptoms and commonly manifested local complications of the disease continued to dissipate comparably to the general state normalization rates in patients subjected to infusion chemotherapy; additionally, catarrhal changes auscultated over the lungs remained in twice as many cases.

Abacillation was observed in 96.6 ± 2.4% patients treated intravenously intermittently and 92.7 ± 3.5% patients treated intravenously daily, while in the control group treated with traditional chemotherapy, 87.5 ± 4.8% patients of these, 82.4 ± 5.1, 81.6 ± 5.3% and 64.3 ± 6.9%, respectively, demonstrated abacillation in the first three months, which means that bacterioexcretion slowing rates were higher under conditions of intravenous tuberculostatic infusions compared to those of traditional chemotherapy. It should be noted that among 215 patients observed by V.G. Kononenko, there were 16 cases of fibrous-cavernous tuberculosis and 3 cases of tuberculoma, which aggravated the therapy results in each of the observed groups.
Cavity closure was observed in 63 out of 74 (85.1 ± 4.1%) patients in the first group, receiving intermittent intravenous therapy; 45 out of 62 (72.6 ± 5.7%) patients in the second group, receiving daily infusion therapy; and in 25 out of 53* (47.2 ± 6.9%) patients in the third group, receiving traditional chemotherapy. During the first 6 months, cavity closure was observed in 64.8 ± 5.6%, 59 ± 6.3% and 17 ± 5.2% patients, respectively, therefore, both the frequency and the rates of cavity closure was considerably higher for infusion therapy compared to traditional therapy. Somewhat worse results of the second group compared to the first were associated with lower average therapy duration due to manifested intolerance of daily infusions and side effects appearing after 3-4 months of such therapy. Such adverse effects were not observed in intermittent therapy.

T.A. Borovitskaya [1982], when comparing the effectiveness of intermittent chemotherapy administered twice and thrice weekly, demonstrated that, given the doubtless quickening and maximum patient abacillation rate, intravenous administration of the regular doses of streptomycin, isoniazid and PAS twice weekly is more effective than thrice.

L.N. Savonenkova [1988] compared the direct results of intermittent chemotherapy in two patient groups, including a total of 150 patients with newly-diagnosed infiltrative (96), disseminated (45) and focal (9) pulmonary tuberculosis in the decay phase or sputum smear-positive, treated in inpatient care for an average of 6.7 ± 0.1 months. The groups were sufficiently representative in terms of pulmonary tuberculosis clinical manifestations, sex, age, concomitant disease frequency and tuberculosis complication.

L.N. Savonenkova established that intoxication symptoms and local disease manifestations dissipated quite quickly in the first group: on average, over 1.3±0.1 and 1.9±0.2 months, respectively. These patients showed quicker recovery compared to the control group in terms of body temperature normalization (2.0±0.2 weeks and 3.3±0.3 weeks), dissipation of bubbling rates over the lungs (1.5±0.2 months and 1.9±1.9 months), and elimination of the left shift of the blood cell differential (1.4±0.3 months and 2.4±0.4 months). Abacillation was achieved in 98.3±1.7% patients in the first and 91.8±3.9% patients in the second group (the difference is not statistically reliable, P>0.1). However, average abacillation time was shorter for isoniazid and PAS treatment combined with rifampicin (1.4±0.1 months) compared to streptomycin (2±0.2 months).

It should be noted that the abacillation rate in fresh destructive processes was equally high in urban or rural dwelling patients, ages 18-49 or above 50, male or female, patients with limited or widespread tuberculosis, while still in inpatient care.

Therefore, treatment of open and destructive tuberculosis was successful in 81.8±4.7% patients in the second group, over 3.5±0.2 months on average. No statistically significant difference was observed in the compared parameters.

Additional surgery was performed in 5 out of 8 patients with incomplete therapeutic effect in the first group, and in 4 out of 12 patients in the second. Therefore, treatment of open and destructive tuberculosis was successful in 96±2.3% patients of the first group and in 89.3±3.5% patients in the second group over the first 6-7 months, while still in inpatient care.

However, treatment tolerability was higher in the main group compared to the control group. Adverse reactions to tuberculosis drugs were manifested by 4.0±2.3% patients of the first group and 16±4.2% patients of the second. Intractable reactions, mainly to streptomycin, were only observed in the second group, in 14.7±4.1% patients.

However, despite the advantages of biweekly intravenous administration of isoniazid and PAS combined with rifampicin capsules over streptomycin in pulmonary tuberculosis patients, as discovered by L.N. Savonenkova, both of these bactericidal methods are valid. At the beginning of the era of intravenous PAS administration, a method for solution preparation and sterilization using Seits filter was suggested. Subsequently, sodium sulfide and rongalite were suggested for PAS solution sterilization. In the 60’s, the Soviet Union was purchasing sterile PAS-sodium powder by Chinoin (Hungary), packaged in dark bottles, and suitable for long storage. The 3% solution prepared with it was suitable for immediate intravenous drop infusion. In the following years, production of PAS for intravenous administration was stopped, which decreased the arsenal of intravenous antituberculosis drugs at the disposal of phthisiologists.

Intravenous Administration of PAS in Tuberculosis Treatment. Over 60 Years of World Experience.

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Currently, Russia has high demand for PAS (para-aminosalicylic acid) for intravenous administration. This treatment has been proven to be highly effective in combination therapy of tuberculosis (affecting the tuberculosis mycobacteria + increasing the effect of the main drug isoniazid + non-specific anti-inflammatory effect). The effectiveness of PAS has been proven by numerous scientific studies and confirmed in wide practice. PAS is recommended for treatment of resistant tuberculosis (Order N109 of the Ministry of HealthCare of the Russian Federation) and is included in the therapeutic regiments of patients observed in follow-up care. Today, approximately 5% of newly-diagnosed patients are patients with "primary" multi-resistant tuberculosis; among the patients observed in follow-up care, a third requires the use of the drug. These patient groups require treatment with PAS.

PAS is a second-line anti-tuberculosis drug (ATB) with a bacteriostatic effect. PAS is active only against M.tuberculosis and does not affect other mycobacteria. The foundation of PAS’s bactericidal effect is its antagonism with PABA, which is a growth factor of M.tuberculosis. PAS affects mycobacteria in the state of active multiplication, and has virtually no effect on mycobacteria in quiescent state. Has little effect on causative agents located intracellularly. Combines well with other ABT. Good tolerability for intravenous intermittent administration. Adult daily dose is 9-12 g. Decreases the likelihood of isoniazid and streptomycin resistance development. When applied together with isoniazid, decreases the latter's acetylation degree.

PAS is accumulated in lymph nodes, the uterus and serous sacs.

Today, 12 major antituberculosis drugs are known in the world, which is insufficient, given the growth of drug-resistant tuberculosis. An intensive chemotherapy course requires simultaneous use of 3 to 6 drugs to which the bacteria are still sensitive. Only this allows effectively impacting the tuberculosis process, including the drug-resistant one, and preventing development of multiple drug resistance of MBT. Considering the prolonged absence of PAS on the antituberculosis drug market, cases of MBT developing resistance to it are rare.

PAS is one of effective combined effect antituberculosis drugs (actually affecting the tuberculosis mycobacteria + increasing the effect of the main drug isoniazid + non-specific anti-inflammatory effect). The effectiveness of PAS has been proven by numerous scientific studies and confirmed in wide practice. PAS is recommended for treatment of multiple-resistant tuberculosis (WHO).

The duration of an intensive therapy course with PAS is 4 months, on average. The drug dose is 12 grams, 2-5 days a week. Therefore, the required amount for one patient's treatment course is between 380 and 960 gram.

The share of patients with multiple-resistant MBT among newly-diagnosed patients with bacillary tuberculosis forms was 8.3% in 2002, according to the Siberian Federal District Area; among patients in follow-up care, this share was 1/3. These patients require treatment using PAS. PAS has been used in tuberculosis treatment since 1946, in the form of sodium or potassium salt.

The first mentions of intravenous administration of PAS to tuberculosis patients were made in publications of J. Paraf et al [1948] and W. R. Barclay [1949]. At the same time, works researching the PAS administration effectiveness when combined with other ATB, have emerged.

H. Lauener and G. Favez [1959] established that PAS allows inhibiting quickened isoniazid inactivation in humans. This was confirmed by P. Schmitz and B. Kleine-Allekotte, who suggested intravenous administration of both drugs combined with streptomycin. F.V. Shebanov [1965] believed that combination therapy of tuberculosis patients, especially in the scope of outpatient care, is impossible without PAS. He highly valued the antimicrobial and anti-inflammatory properties of this drug.

M. Kagamiyama and M. Majima, studying the free isoniazid concentration 2-4-6 hours after oral administration of 0.2 g of the drug discovered that the presence of PAS affects the blood content of specifically free isoniazid, as opposed to total isoniazid blood content – because PAS, due to its competitiveness, inhibits isoniazid inactivation.