INTENSIVE TREATMENT OF TUBERCULOSIS. NEW POSSIBILITIES

the book of abstracts (2006-2013)

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Attempts to treat tuberculosis intravenously have been started in early XX century. But at the beginning of this century the international medical TB community uses mainly “per os” and intramuscular administration of TB drugs. Main TB treatment recommendations from respected international medical expert groups leave IV route only for critically or severely ill TB patients. Pharmaceutical achievements in preparation of IV forms of TB medications, improved IV techniques, observed limitations of “per os” TB treatment, deeper understanding of TB disease epidemiology and collected TB control program experience from recent world-wide WHO-led activities – all these points made us to try to revise IV aspects of TB treatment effectiveness. We narrowed possible advantages of IV treatment as it:

1) Ensures direct observation of the treatment
2) Helps to provide and to calculate precise dosage to each TB patient
3) Increases medical level of health care delivery
4) Increases level of technology, applied for basic TB treatment
5) Helps TB patient to avoid appearance, taste, smell of medications and all process of swallowing of impressive daily handful amount of tablets
6) Has fewer adverse reactions.

Last two items positively influence TB treatment adherence

Methods: It was a prospective randomized cohort study. Total of 224 TB patients were enrolled. 95 patients of them were without hepatitis, 129 patients with hepatitis B and C (58 – B, 29 – C, 42 – B&C). Researchers have divided them into another 3 groups by treatment regimen – IV intermittent, standard daily and irregular.

Results: Statistically significant difference in increase of cavity closure and reduced rate of adverse effects in IV intermittent group.

Conclusion: IV positive results must be investigated further.
INTERMITTENT INTRAVENOUS CHEMOTHERAPY IN NEW CASES OF PULMONARY TUBERCULOSIS

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The purpose: To compare the efficacy and tolerability of intermittent intravenous and daily traditional treatment in patients with new cases of pulmonary tuberculosis.

Methods: We have conducted a randomized comparative prospective study of daily per os vs. intravenous intermittent chemotherapy for 74 new cases TB with smear positivity (MBT+). We have randomized those patients into 2 groups: Group #1 – 23 people – received standard chemotherapy every day; Group #2 – 51 people – received intravenously two times a week isoniazid 12 mg/kg, rifampicin 7.5-10 mg/kg, intramuscular streptomycin 16 mg/kg, per os pyrazinamide 25 mg/kg. Groups were identical by sex, age, and form of disease. There were 5 patients in the first group and 9 patients in the second with MDR-TB.

Results: Cavity closed in 18 patients of the group #1 and 45 of the group #2 (P<0.05), sputum negativation occurred in 20 and 45 (P>0.05) correspondingly.

Toxic reactions occurred in 16 and 4 patients accordingly (RR=8.9, 95% CI 6.9-10.8; P=0.000001). It was found that at patients with toxic reactions to chemotherapy in the group #1 cavity closed in 7.3±1.3 months, and in the group #2 at 2.5±0.9 months (P=0.02, log-rank test Mantel-Cox).

Conclusion: The intermittent intravenous chemotherapy for new patients with pulmonary tuberculosis is effective and preventive with occurrence of toxic reactions in comparison with a daily treatment per os: toxic reactions in group of TB patients with the daily per os treatment were worse than in group of patients on intermittent intravenous treatment.

THE PHARMACOTHERAPY OPTIONS FOR THE INTENSIVE TREATMENT PHASE IN PATIENTS WITH PRIMARILY DIAGNOSED PULMONARY TUBERCULOSIS

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The purpose: To improve the efficacy of treatment of patients with primarily diagnosed pulmonary tuberculosis via optimization of treatment protocols for the intensive phase of anti-TB therapy.

Methods: 60 patients, with primarily diagnosed pulmonary tuberculosis were distributed into the main (MG) and control (CG) groups. As complex therapy, the patients of the MG received isoniazid, rifamycin and ethambutol intravenously, pyrazinamide orally and streptomycin IM. The patients of the CG were administered standardized oral therapy with isoniazid, rifampicin, ethambutol and pyrazinamide and streptomycin IM.

Results: In complex parenteral administration of isoniazid, rifamycin and ethambutol a trend was noted towards 25% higher indices of bacteriostatic blood activity as compared with the oral anti-TB therapy. In patients of the MG, intensive therapy phase, the sputum was rendered bacillus-free 20.0% more frequently; these patients were typically found to heal decay cavities better – healing occurred in 54.5% versus 40.9% patients on oral treatment during the intensive phase. In pharmacokinetic studies it was estimated that the maximal concentration of rifamycin after single IV dose of 450-600 mg was 22.9±2.3 mg/ml, which is significantly higher than rifampicin concentration in oral administration at the dose of 450-600 mg (8.9±1.3 mg/ml, p<0.05).

Conclusion: Intravenous administration of rifamycin, ethambutol and isoniazid in the intensive phase of chemotherapy results in reduction of the amount of time, required for bacillus-free rendering of sputum and faster healing of decay cavities in patients with primarily diagnosed pulmonary tuberculosis.

Abstract book of the 22nd ERS Congress (1-5 September 2012, Vienna, Austria)
INTENSIFIED REGIMEN CONTAINING RIFAMPICIN AND MOXIFLOXACIN FOR TUBERCULOUS MENINGITIS: AN OPEN-LABEL, RANDOMIZED CONTROLLED PHASE 2 TRIAL

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Background: Intensified antibiotic treatment might improve the outcome of tuberculous meningitis. We assessed pharmacokinetics, safety, and survival benefit of several treatment regimens containing high-dose rifampicin and moxifloxacin in patients with tuberculous meningitis in a hospital setting.

Methods: In an open-label, phase 2 trial with a factorial design in one hospital in Indonesia, patients (aged>14 years) with tuberculous meningitis were randomly assigned to receive, according to a computer-generated schedule, first rifampicin standard dose (450 mg, about 10 mg/kg) orally or high dose (600 mg, about 13 mg/kg) intravenously, and second oral moxifloxacin 400 mg, moxifloxacin 800 mg, or ethambutol 750 mg once daily. All patients were given standard-dose isoniazid, pyrazinamide, and adjunctive corticosteroids. After 14 days of treatment all patients continued with standard treatment for tuberculosis. Endpoints included pharmacokinetic analyses of the blood and cerebrospinal fluid, adverse events attributable to tuberculosis treatment, and survival. Analysis was by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT01158755.

Findings: 60 patients were randomly assigned to receive rifampicin standard dose (12 no moxifloxacin, ten moxifloxacin 400 mg, and nine moxifloxacin 800 mg) and high dose (ten no moxifloxacin, nine moxifloxacin 400 mg, and ten moxifloxacin 800 mg). A 33% higher dose of rifampicin, intravenously, led to a three times higher geometric mean area under the time-concentration curve up to 6 h after dose (AUC_{0-6h}; 78.7 mg*h/L [95% CI 71.0-87.3] vs 26.0 mg*h/L [19.0-35.6]), maximum plasma concentrations (C_{max}; 22.1 mg/L [19.9-24.6] vs 6.3 mg/L [4.9-8.3]), and concentrations in cerebrospinal fluid (0.60 mg/L [0.46-0.78] vs 0.21 mg/L [0.16-0.27]). Doubling the dose of moxifloxacin resulted in a proportional increase in plasma AUC_{0-6h} (31.5 mg*h/L [24.1-41.1] vs 15.1 mg*h/L [12.8-17.7]), C_{max} (7.4 mg/L [5.6-9.6] vs 3.9 mg/L [3.2-4.8]), and drug concentrations in cerebrospinal fluid (2.43 mg/L [1.81-3.27] vs 1.52 mg/L [1.28-1.82]). Intensified treatment did not result in increased toxicity. 6 month mortality was substantially lower in patients given high-dose rifampicin intravenously (ten [35%] vs 20 [65%]), which could not be explained by HIV status or severity of disease at the time of presentation (adjusted HR 0.42; 95% CI 0.20-0.91; p=0.03).

Interpretation: These data suggest that treatment containing a higher dose of rifampicin and standard-dose or high-dose moxifloxacin during the first 2 weeks is safe in patients with tuberculous meningitis, and that high-dose intravenous rifampicin could be associated with a survival benefit in patients with severe disease.

THE EFFICACY OF TREATMENT OF PATIENTS WITH MULTIDRUG-RESISTANT PULMONARY TUBERCULOSIS WITH APPLICATION OF INTRAVENOUS ETHAMBUTOL WITHIN THE SCHEDULES OF THE INTENSIVE PHASE OF CHEMOTHERAPY

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Background: The treatment of patients with multidrug-resistant pulmonary tuberculosis (MDR TB) is closely linked with the intensive chemotherapeutic schedules of both oral and intravenous anti-tuberculosis drugs (ATD). The intravenous route of PAS administration produced somewhat less frequent dyspepsia, compared to oral route, whereas the efficacy of both methods was quite close, with insignificant advantage of the intravenous therapy. It is also noteworthy that the authors recommend intravenous administration of the drug at the initial stage of the intensive phase of chemotherapy, after which conversion to oral administration is possible.

At the same time, the evidence is lacking in literature concerning the efficacy of intravenous ethambutol compared to oral route. According to the international standards of treatment of patients with MDR TB, the main administration route for ethambutol is oral; the injection route of ATD administration is recommended only for aminoglycosides. It is believed that the injection route of ATD administration is recommended in patients with low treatment compliance, which ensures guaranteed treatment control in such patients. Therefore, the aim of the work is to evaluate clinical efficacy of conventional therapeutic doses of ethambutol (15 mg/kg), as a component of the intensive phase of chemotherapy via daily oral administration compared with intravenous administration of the drug in patients with multi-resistant pulmonary tuberculosis.

Methods: The regimen of the intensive phase of chemotherapy with inclusion of ethambutol in most patients was structured as follows: ethambutol + pyrazinamide + levofloxacin + kanamycin + PAS + ethionamide (EZLfxK-PasEt) daily for 4 months. Patients with MDR TB (n=72) were distributed into groups by pair matching method: main group (Group I), where conventional therapeutic doses (15 mg/kg) of ethambutol were administered for 4 months via intravenous route (36 patients) in the regimen of the intensive phase of chemotherapy and the comparator group (Group II), where ethambutol was administered orally (36 patients).

Results: The rates of cessation of clinical manifestations of the disease and abacillation are accelerated by 25.0%, which equals 0.8 months, that is, 24 days. Taking into consideration that the term of in-patient treatment in patients with MDR TB should be completed after abacillation, the intravenous use of ethambutol, compared to oral administration, allows the discharge of patients with MDR TB almost a month faster. In Ukraine, the average per-bed daily hospital expenditures are 16.60 UAH for sustenance and 260 UAH for hospital bed maintenance, adding up to 276.60 UAH. Thus, reduction of hospital stay by 0.8 months allows saving
6638.40 UAH per each patient. In Group I cessation of infiltrative and focal pulmonary lesions was observed in 9 (25.0%) patients, healing of caverns — in 11 (30.6%) patients, whereas in Group II, respectively, in 7 (19.5%) and 8 (22.2%) patients, which is 5.5% and 8.4% less (p>0.05). The tolerability of treatment schedules of the intensive phase of chemotherapy in administration of conventional therapeutic doses of ethambutol in patients of Group I and II was the following: by and large, adverse events due to administration of ATDs in the intensive phase of chemotherapy had occurred in 5 (13.9%) patients of Group I vs. 7 (19.4%) patients of Group II (p>0.05) due to the development of hepatotoxic (5.5% and 8.3%, respectively, in groups compared), dyspeptic (5.5% in both groups compared) and ototoxic reactions (2.7% in both groups compared); an allergic reaction developed in 1 (2.8%) patient of Group I. Therefore, the tolerability of ethambutol in the schedules of the intensive phase of chemotherapy in case of its both oral and intravenous administration, proved to be equally good. No ethambutol-specific vision-related adverse events were observed.

Conclusion: Intravenous administration of conventional therapeutic doses of ethambutol (15 mg/kg) within multi-modality treatment of patients with MDR TB in the intensive phase of chemotherapy allows increasing the efficacy of treatment in such patients, which allows discharging the patients to continue treatment in an out-patient mode.

EFFICIENCY AND TOLERABILITY OF INJECTABLE PAS IN THE INDIVIDUALIZED REGIMENS OF CHEMOTHERAPY FOR THE TREATMENT OF PATIENTS WITH MULTIDRUG-RESISTANT TUBERCULOSIS

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Background: In severe infections parenteral administration of antibiotics is preferable. Parenteral infusions ensure exact dosage that does not depend on the gastrointestinal system condition, i.e., absorption, and rapid effect with formation of the maximum concentrations is achieved. In the case of intravenous administration higher levels of drug concentration in the blood are created regardless on the patient’s condition and that enhances its penetration into the tissues. The aim of the research was to improve treatment of patients with MDR TB by injectable PAS prescription in individualized chemotherapy regimens.

Methods: In an open, randomized, controlled clinical trial 60 patients with MDR tuberculosis were involved. Patients of the main group (30 persons) received chemotherapy regimen with inclusion of injectable PAS and registered in Ukraine drugs of the 1st and 2nd lines, patients of the control group (30 persons) – oral form of PAS as an intestinal soluble granules. Most patients (85.0%) of both groups 5 anti-TB drugs were administered every day, to which MBT was sensitive: ethambutol + pyrazinamide + levofloxacin + kanamycin + PAS. Other patients because of the resistance of Mycobacterium tuberculosis to some of these remedies received another 5 component chemotherapy regimens, which included capreomycin, terizidon, protonamide. All patients in this study received PAS in a daily single dose of 12 g as intravenous or oral administration as well. Dosage adjustment was performed in connection with the occurrence of adverse reactions.

Results: At the end of the intensive phase of chemotherapy significant improvement was not founded in 4.3% of patients who received PAS intravenously vs. 26.7% of patients who took the remedy orally (p <0,05).

Improved effectiveness of treatment was due to better tolerability of intravenous PAS compared with oral one. In the case of oral PAS usage in 26.7% of patients to overcome serious adverse reactions was necessary to reduce the dose or to withdrawal the drug, whereas during the intravenous administration of PAS due to possibility to control infusion rate such actions were not carried out.

Conclusion: Results of the study showed that inclusion of an intravenous form of PAS into the chemotherapy regimen in its intensive phase for patients with MDR tuberculosis increases the effectiveness of treatment by accelerating the term of bacteria expulsion cessation and disappearance of clinical symptoms, respectively by 14.4 and 18.2%. The term of bacteria expulsion cessation in patients who received injectable PAS, compared with oral one, was 4.7 versus 5.8 months, which allowed them to make stationary phase of treatment shorter in 1.1 month.
EFFECTIVENESS OF INTRAVENOUS PAS IN THE TREATMENT OF PATIENTS WITH DESTRUCTIVE RESISTANT PULMONARY TUBERCULOSIS


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Background: The purpose of the study was to determine the effectiveness of PAS in the complex chemotherapy of chemoresistant destructive pulmonary tuberculosis (mostly chronic) and opportunities to prevent or reduce adverse effects while receiving PAS.

Methods: The study involved 82 patients with destructive pulmonary tuberculosis. For intravenous usage of PAS was prescribed Paskonat (Yuria-Pharm, Ukraine) – 3% solution of sodium para-aminosalicylate for infusion, in vials of 400 ml. The daily dose of PAS (12 g of sodium para-aminosalicylate in 400 ml of 3% solution) was infused mainly during 1.5-2 hours with a rate of infusion up to 40-60 drops per minute. The drug was administered by intermittent method (every other day or 3 times a week). PAS also was prescribed orally as intestinal soluble granules in a daily dose preferably 12 g, rarely – 8-12 g (the rate of 150-200 mg per 1 kg of body weight), 0.5-2.5 hours after a meal, 1-2 times a day, every day or by an intermittent method. In general, only intravenous route of PAS administration was used in 39 patients, only oral – in 16 and both ways – in 27 people. PAS was administered in combination with 3-5 or more anti-TB drugs, to which MTB retained sensitivity and / or were not previously used or were prescribed for a short period.

Results: A complex chemotherapy with PAS inclusion allowed to note presence of a significant improvement (healing of caverns, absence of bacilli and elimination of other manifestations of active TB) in 31 (37.8%) patients, improvement (cessation or absence of bacteria expulsion, partial regression of cavities, liquidation or significant reduction of other manifestations of the disease) – in 18 (21.9%), partial improvement (symptomatic, as well as mild resolution of focal and infiltrative foci and partial regression of cavities and reduction of massiveness of bacteria expulsion) – in 19 (23.2%) and the pattern of the disease was not improved significantly in 8 (9.7%) patients with serious chronic multiple caverns and multi-drug-resistance to 5-9 drugs. Thus, in most patients (48 (58.5%)) with rather severe process were obtained substantial positive outcomes of chemotherapy and PAS was a significant factor of that. Depending on which route of drug administration patients used significantly longer, they were referred to the appropriate group. Therefore, among 48 patients who received PAS only or mainly intravenously (among them 47 expelled MTB), bacterial excretion ceased in 28 (59.6%) people, and cavities were healed in 19 (39.6%). Among 22 patients with exclusively or predominantly oral PAS administration were not detected in 11 of 21 those who expelled bacteria (52.4%), and destructive cavities were healed in 7 (31.8%). Partial regression of cavities after intravenous and oral administration of PAS was defined respectively in 22 (45.8%) and 9 (40.9%) patients. Thus, both methods effectiveness are very close, it may be noted only a slight tendency to better results in the case of intravenous PAS usage most likely due to a higher drug concentration in the blood.

Conclusion: Together with other reserve anti-TB drugs PAS is able to take its significant place in the chemotherapy of patients with destructive chemoresistant pulmonary tuberculosis.

RESULTS OF PAS APPLICATION IN COMPLEX CHEMOTHERAPY OF PATIENTS WITH DESTRUCTIVE, INEFFECTIVELY TREATED PREVIOUSLY, RESISTANT PULMONARY TUBERCULOSIS

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Background: For decades PAS was almost not used in chemotherapy of tuberculosis, as more effective basic drugs were used in that time (rifampicin, isoniazid, streptomycin, ethambutol, pyrazinamide) as well as some second-line drugs. In recent years, due to the increase of multi- and poli-drug resistance of MBT (MDR-TB, PDR-TB) phthisiatricians’ attention is paid again to PAS (Para-Aminosalicylate Sodium) – one of the first TB drugs widely used in 40-70s of the last century. But still there are virtually no works about the effectiveness and therapeutic opportunities of PAS use for this patients, and in general in patients with previously treated ineffectively, mainly chronic destructive pulmonary tuberculosis.

Methods: The treatment with PAS was performed in 70 patients with destructive pulmonary tuberculosis. In 39 of them (55.7%) there was a chronic destructive process with duration of from 2 to 20 years, treated earlier for a long time or ineffectively, with MDR-MBT (4 outpatient category). In 16 persons (22.9%) with tuberculosis duration from 6 to 24 months destructive process was previously treated ineffectively, it was often accompanied by a multi- or poliresistance of MBT (2nd category). In 6 patients (8.6%) recurrence of destructive tuberculosis was detected (also 2nd category). PAS was used intravenously as well as by oral route. In general, PAS was used only intravenously in 35 patients, only per os – in 12 and by both ways – in 23 (as a rule intravenously at a start and then per os, rarely – vice versa or simultaneously: on some days – intravenously, on other days - per os). PAS was administered in a combination with 3-5 or more anti-TB drugs to which sensitivity of MBT were detected and (or) that were not previously used or used for a short period of time. Most often these drugs were fluoroquinolones, clarithromycin, amikacin, kanamycin, ethambutol, ethionamide (prothionamide), sometimes pyrazinamide, rifabutin, doxycycline and amoxiclav, very rare – isoniazid and rifampicin. These drugs were administered in usual dosage daily or intermittently (every other day, 2-3 times per week). PAS was used in 15 patients for 2-3 months, in 20 – for 3.5-5 months, in 19 – for 5-6 months and in 16 – for 7-12 months.

Results: Direct results of complex chemotherapy with inclusion of PAS were following: in 26 patients (37.1%) – a significant improvement (healing of cavities, negative culture and elimination of other manifestations of active TB), in 15 (21.4%) – improvement (decrease of MBT amount or negative culture/smear, partial regression of cavities, the elimination or significant reduction of other manifestations of the process), in 19 (27.2%) – partial improvement (mainly symptomatic and partial resorption of infiltrative formations, often some regression of cavities and reducing of MBT amount), and in 10 (14.3%) patients with severe chronic polycavernous process and multi-drug resistance to 5-9 drugs course of the disease has not improved: in 8 of them (11.4%) it has not significantly changed, and in 2 (2.9%) it has deteriorated. Thus, in a most patients with very severe process – 41 (58.6%) – positive results were
obtained after chemotherapy containing PAS. The main side effects of PAS were gastro-intestinal disorders: nausea, belching, heartburn, appetite loss, rarely vomiting, abdominal pain, flatulence, diarrhea. These effects occurred predominantly at 1st months of treatment, sometimes at 2-3d months and later, they were of different intensity and duration (from several days to 1-3 months).

1. The results of the PAS use in the complex chemotherapy in patients with destructive, previously treated ineffectively, resistant TB of the lungs are significant: negative culture in 57.4% of people, cavity healed in 37.1% and partially regressed – in 44.3%, which accordingly is by 17.4%, 7.9% and 8.2% respectively higher than in chemotherapy regimens without the use of PAS. Terms of disappearance of MBT and cavities were shortened by 1 month.

2. PAS relatively often causes side effects (were recorded in 32.9% of patients), mainly GI (in 25.7%); in 14.3% of persons severe reactions were observed that disappeared rapidly after drug withdrawal.

3. Intravenous administration of PAS (Paskonat) somewhat less often provoked dyspeptic effects (20.7% of cases) than oral one (in 31.4%). The effectiveness of both methods is very close, with a slight advantage of intravenous one. This method is most appropriate to apply in the first phase of intensive chemotherapy, and then it can be switched to oral administration.

4. To improve PAS tolerability it is necessary to follow the contraindications for its use, have appropriate three regular meals, slow (at least for 1.5–2 hours) intravenous administration of a drug, taking per os in 0.5–2.5 hours after eating and in different time with other medicines that also can cause GI side effects, switching to the intermittent mode of administration. Intermittent method reduces GI disorders at least 2 times and has almost the same effectiveness as everyday use.

5. PAS has a high ability to prevent development of resistance to the anti-TB drugs, which are combined with this drug. Besides, we observed no one case of resistance to PAS development.

6. PAS along with other reserve drugs may take an important place in chemotherapy of destructive, previously treated ineffectively, resistant TB of the lungs.

_Ukrainian Pulmonological Journal, 2006, №1_

**Conclusion:**

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5. PAS has a high ability to prevent development of resistance to the anti-TB drugs, which are combined with this drug. Besides, we observed no one case of resistance to PAS development.

6. PAS along with other reserve drugs may take an important place in chemotherapy of destructive, previously treated ineffectively, resistant TB of the lungs.
THE TOLERABILITY OF A COMBINATION OF INJECTABLE ANTITUBERCULOSIS DRUGS IN CUSTOMIZED CHEMOTHERAPEUTIC SCHEDULES IN TREATMENT OF PATIENTS WITH MULTIDRUG-RESISTANT PULMONARY TUBERCULOSIS

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Background: According to the international standards that define treatment of patients with multidrug-resistant pulmonary tuberculosis (MDR-TB), the main route of administration of antituberculosis drugs is oral; injections are reserved only for aminoglycosides. As of today the quantity of injectable antituberculosis drugs has increased, which allows simultaneous administration of 4 products in patients with MDR-TB, namely ethambutol, a fluoroquinolone (ofloxacin, levofloxacin, gatifloxacin or moxifloxacin), an aminoglycoside (kanamycin, amikacin) and PAS. The aim of the study was to evaluate the tolerability of the combination of injectable antituberculosis drugs in customized chemotherapy schedules in treatment of patients with multidrug-resistant pulmonary tuberculosis.

Methods: A randomized controlled trial compared the efficacy of two chemotherapy regimens for the treatment of patients with MDR-TB with injectable and oral antituberculosis therapies, which included five antituberculosis drugs – ethambutol, pyrazinamide, kanamycin, levofloxacin and PAS. The difference between the chemotherapy regimens was intravenous administration of ethambutol (25 mg/kg), levofloxacin (15 mg/kg) and PAS (150 mg/kg) in patients of the main group, whereas patients of the control group took the same drugs orally in identical single daily doses. Amikacin was the fourth drug of the chemotherapy regimen in patients of both groups (intramuscularly at 15 mg/kg), and pyrazinamide was the fifth drug in both groups (orally at 25 mg/kg). All drugs were administered simultaneously in the a.m. The study groups (the main group and the control group) included 30 subjects each and were identical in terms of duration and severity of the tuberculosis process, as well as the assigned chemotherapy regimens, since both patient groups were comparable by the profile of MTB drug resistance. All patients had advanced destructive pulmonary process with one or more caverns and an identical profile of MTB drug resistance MTB to, mainly, 3-4 antituberculosis drugs (86.7%). No extended MTB resistance to antituberculosis drugs was found in any of the study groups.

Results: Gastrointestinal reactions were leading moderate adverse events in patients of both groups. However, these manifestations were significantly (p<0.05) more frequent in patients of the control group – 40.0% cases vs. 16.7% cases in the control group. Therefore, the patients of the main group receiving intravenous antituberculosis drugs developed 58.3% less gastrointestinal adverse reactions.

Conclusion: The application of a combination of intravenous antituberculosis drugs during the intensive phase of chemotherapy in patients with MDR-TB allows reducing the incidence of severe gastrointestinal events 2.3 times. In severe adverse events due to application of intravenous drugs the average treatment interruption was 2 times shorter, than in oral treatment and was equal to 3.7±0.6 days.

Ukrainian Chemotherapy Journal, Issue No. 3(26) – 2012
TOLERABILITY OF INTENSIVE CHEMOTHERAPY IN APPLYING INTRAVENOUS AND ORAL FORMS OF ANTI-TB DRUGS IN PATIENTS WITH MDR-TB

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**Background:** Poor tolerability of II-nd line anti-TB drugs is the most common cause of poor results of treatment because of interruption of treatment due to the big number of drugs in chemotherapy regimens and dosage or serious adverse reactions, which leads to the spread of drug resistance of Mycobacterium tuberculosis and the formation of incurable forms of the disease.

**Methods:** The frequency of adverse reactions during the intensive phase of chemotherapy was studied in 140 patients with MDR-TB in the application of intravenous (main group, n=70) and oral (control group, n=70) forms of anti-TB drugs. In patients of main group ethambutol (20 mg/kg), levofloxacin (15 mg/kg), PAS (150 mg/kg) were used intravenously, in the control group these drugs in the same doses were used orally. The fourth drug in chemotherapy regimens in patients of both groups was amikacin (15 mg/kg) intramuscularly, fifth – pyrazinamide (25 mg/kg) – orally. All drugs used simultaneously in the morning.

**Results:** Among moderate adverse events in both groups the most frequent were gastrointestinal reactions and a moderate increase in alanine aminotransferase. However, these manifestations were significantly more frequent in the control group – 22 (31.4%) vs. 12 (17.1%) cases in the main group, p<0.05. Thus, in the main group, where intravenous anti-TB drugs were used, by 39.3% less adverse reactions occured. Serious adverse reactions that required discontinuation of chemotherapy was observed in 3 (4.2%) patients of the main group: ototoxic reaction of amikacin in 1 patient, allergic reactions such as severe dermatitis of pyrazinamide – in 1 patient, diarrhea from PAS – in 1 patient. After discontinuation of these drugs adverse reactions did not restore. In the control group of patients who were treated with oral forms of anti-TB drugs significantly more serious adverse reactions was seen – in 10 (14.3%) patients. 1 patient had severe hepatotoxic reaction in 2 patients – allergic, 7 patients had vomiting, diarrhea, abdominal pain after taking the tablet forms of drugs and PAS in the form of enteric-soluble granules.

Severe adverse reactions in patients of the main group occurred in 3.4 times less than in the control group.

**Conclusion:** The use of a combination of intravenous forms of TB drugs in the intensive phase of chemotherapy in patients with MDR-TB can reduce the incidence of adverse reactions to 39.3%, severe reactions – in 3.4 times. In the main group where intravenous drugs were used medium term interruption of treatment was 2 times less than when taking tablets.

*Collected works of employees of NMAPE n.a. P.L. Shupyk, Issue No. 19 (3) - 2010, page 741-745*
EFFECTIVENESS OF INTRAVENOUS PAS IN PATIENTS WITH MDR-TB IN THE INTENSIVE PHASE OF CHEMOTHERAPY

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Background: Treatment of patients with MDR-TB requires intensive treatment at the start of chemotherapy to accelerate termination of bacteria to prevent further spread of resistance of Mycobacterium tuberculosis. The intravenous administration of anti-TB drugs is recommended in patients with diseases of the gastrointestinal tract, low adherence to treatment due to better tolerability which guaranteed continuous controlled treatment. In Ukraine available several forms of intravenous II-nd line anti-TB drugs, including para-aminosalicylate sodium (PAS), which refers to drugs with moderate activity and is characterized with numerous side effects that prevent the full carrying anti-TB chemotherapy.

The aim of this study was to establish clinical efficacy and tolerability of PAS (200 mg / kg) in the intensive phase of chemotherapy via intravenous and oral administration.

Methods: All patients with MDR-TB (n=144) were divided into two groups: main (n=72), in which PAS was used via intravenous infusion in the intensive phase of chemotherapy (6 months) and control (n=72) where PAS was used per os (enteric granules). Most of the patients (87.5%) were resistant to 4 and more anti-TB drugs. Among them, almost half of the patients (48.6%) were resistant to 4-5 anti-TB drugs.

Abacillation was achieved in 52 (72.2%) patients of main group compared to 48 (62.5%) patients of control, that was 9.7% higher, although not significant difference obtained (p> 0.05). The same trend can be seen in frequency and timing of disappearance of clinical manifestations of the disease, allowing patients to prescribe outpatient treatment. However, the use of intravenous form of PAS led to the probable reducing time of stationary phase of treatment by almost 1 month. Consequently, tolerability of intravenous PAS was significantly better than receiving this drug inside as enteric granules.

Results: Abacillation was achieved in 52 (72.2%) patients of main group compared to 48 (62.5%) patients of control, that was 9.7% higher, although not significant difference obtained (p> 0.05). The same trend can be seen in frequency and timing of disappearance of clinical manifestations of the disease, allowing patients to prescribe outpatient treatment. However, the use of intravenous form of PAS led to the probable reducing time of stationary phase of treatment by almost 1 month. Consequently, tolerability of intravenous PAS was significantly better than receiving this drug inside as enteric granules.

Conclusion: Including the intravenous form of PAS in the chemotherapy regimen for patients with MDR-TB on intensive phase of treatment increases the treatment efficiency by speeding up the rate of abacillation and disappearance of clinical symptoms. Improving the effectiveness of treatment due to better tolerability of intravenous method comparing to oral led to possibility to reduce the dose of PAS in 26.4% of patients.

Collected works of employees of NMAPE n.a. P.L. Shupyk, Issue No. 19 (2) - 2010, page 257-263
APPLICATION OF LEVOFLOXACIN IN THE TREATMENT OF PATIENTS WITH MENINGOENCEPHALITIS OF TUBERCULOUS ORIGIN


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Background: Tuberculous meningoencephalitis remains one of the most challenging varieties in terms of both diagnosis and treatment. The presence of non-specific opportunistic bacterial flora is recognized as one of the factors aggravating the course of the disease and its diagnosis. There are reports that in late onset of specific therapy in patients with tuberculous meningoencephalitis (more than 2 weeks since the initial clinical manifestations of the disease) the mortality rates reach 100%, despite the utilization of all contemporary protocols of intensive therapy.

The aim of the study is to improve the results of intensive therapy in patients with late diagnosed tuberculous meningoencephalitis resistant to conventional therapy due to the inclusion of combined (intravenous and intrathecal) administration levofloxacin to therapeutic schedules.

Methods: A total of 12 patients of young and middle age were under observation. In 8 of 12 patients meningoencephalitis developed at the background of HIV infection. The duration of the disease was over 1 month. In clinical terms all patients had signs of intoxication, general cerebral and focal affections of the brain (predominantly stem structures), hypertension of cerebrospinal fluid (CSF) and meningeal syndrome. CSF had changes typical of tuberculous meningitis: pleocytosis (198.2±33.8 cells per power field) with predominating lymphocytes (62.7±4.8%), protein levels of 3.34±0.19 g/L (mainly due to the large molecular fraction) and increased CSF pressure (480+150 mm H2O). The syndrome of multiple organ failure (with pulmonary, renal, hepatic and cardiac failure) was present in 10 of 12 patients. One or two weeks of standard antituberculosis therapy (in accordance with WHO guidelines), initiated at the peak of clinical manifestations of meningoencephalitis (Week 3-6), failed to produce any favourable therapeutic response. Pleocytosis and increased CSF protein remained at background levels or even increased (in 3 of 12 patients); CSF hypertension was advancing in all patients.

In order to potentiate the therapeutic effect we used Leflocin both via intravenous and intrathecal route. Levofloxacin (Leflocin, “YURIA-PHARM”, Ukraine) was administered in a conventional way at a daily dose of 1000 mg. For intrathecal administration the product was diluted with normal saline in a 1:2 ratio (3-5 mL of the product + 5-10 mL of normal saline). The above volume was mixed with 3-5 mL of CSF and slowly infused via endolumbar access while monitoring CSF pressure. The number of procedures per course of treatment was 5-10 on the average. The pathogenesis-targeted therapy included infusions of drugs regulating systemic circulation, hormones, detoxification infusion therapy and vitamin therapy.

Results: After analysis of patients’ condition by the end of Week 2 (after 4-5 intrathecal infusions) at the background of combined therapy with levofloxacin, we noted positive changes of neurological status in 9 of 12 patients: general
cerebral symptoms became less pronounced, focal changes were partially decreased as well, albeit to a comparatively lesser degree; CSF changes had a reverse trend (pleocytosis reduced by 25.6±5.4%, protein decreased by 20.5±4.4%, CSF pressure decreased to 210±40 mm H20). Also, general toxicity symptoms were alleviated (reduction of hyperthermia, weakness, intestinal dyskinesia and increased appetite).

When analysing the patients’ condition by Week 4-5 of therapy (after 6-10 intrathecal infusions) positive trends were noted in 10 of 12 patients at the background of combined therapy. As for neurological status, further decrease of general cerebral and focal symptoms was observed. CSF pleocytosis decreased by 76.6±8.6%, CSF protein decreased by 52.8±5.7% and CSF pressure dropped to 180±20 mm H20. General toxicity symptoms were substantially reduced in 7 of 12 patients.

Patient follow-up for 2-3 months indicated the stable reversal of pathological neurological symptoms and general intoxication syndrome (in 10 of 12 patients) with gradual disinfection of CSF, decrease of pleocytosis below 15 cells per power field (mainly due to lymphocytes, in 7 subjects) and reduction of protein levels to 0.45 g/L (in 6 subjects). Further intrathecal administration was conducted in 5 patients.

6 patients were transferred to specialized in-patient institutions in a stable condition. 4 subjects remained in the clinic until complete recovery (mostly patients with HIV infection). Lethal outcomes had occurred in 2 patients at Month 3 and 4 of treatment.

Conclusion: The utilization of combined intravenous and intrathecal administration of levofloxacin as a constituent of conventional therapy in patients with tuberculous meningoencephalitis allows increasing the efficacy of treatment.


Ukrainian Chemotherapy Journal, Issue No. 3(26) - 2012
THE EFFICACY AND TOLERABILITY OF THE INJECTION FORM OF LEVOFLOXACIN IN CUSTOMIZED CHEMOTHERAPEUTIC SCHEDULES IN THE THERAPY OF PATIENTS WITH MULTIDRUG-RESISTANT TUBERCULOSIS

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Background: The efficacy of treatment in patients with expanded-resistance mycobacterium tuberculosis (XDR-TB) remains low. One of the promising trends of improving the therapeutic approaches in MDR-TB patients is determination of optimal administration routes of anti-tuberculosis drugs in order to enhance bacteriostatic and bactericidal concentrations of the latter in body tissues. Parenteral administration of antibiotics is a preferred approach in severe infections. Parenteral infusions provide for exact dosing, independent of the condition of the gastrointestinal system (hence, absorption) and a rapid effect with creation of maximal concentrations. Regardless of patient’s condition, intravenous administration creates higher serum concentrations of the agent, therefore enhancing tissue penetration of the latter, which can be effective in patients with XDR-TB.

Methods: The aim of the study is to evaluate the efficacy and tolerability of the injection form of levofloxacin as a part of customized chemotherapy schedules in patients with MDR-TB. This open-label randomized controlled clinical trial involved 60 patients with MDR-TB. The main group (30 patients) was on chemotherapy schedule with injection Lfx and 1st/2nd line ATA, registered in Ukraine. In the other 30 patients (the group of comparison) oral Lfx was used.

Results: Completion bacterial secretion stopped in 20 (66.7%) patients of the main group compared to 18 (60.0%) patients of the control group, which is 10.0% more; however, no significant difference was obtained due to a small number of observations in the groups of comparison (p > 0.05). However, the application of intravenous Lfx caused a significant acceleration of cessation of bacterial secretion, which allowed shortening the in-patient phase of the treatment by 27 days. The same trend is found with the incidence and terms of cessation of clinical manifestations of the disease, clinical symptoms disappeared in 70.0% and 66.7% patients (p>0.05) in 4.8±0.3 and 5.5±0.2 months, respectively, which is 21 days less on the average.

Conclusion: Increasing the efficacy of treatment in patients with MDR-TB in intravenous administration of Lfx occurs only in terms of increased rates of cessation of bacterial secretion (by 18.0%) and elimination of clinical symptoms of tuberculosis (by 12.8%), which allowed shortening the in-patient phase of treatment by 21 days on the average. Intravenous administration of Lfx does not affect the tolerability of multimodality anti-tuberculosis therapy. The incidence of adverse events is the same for intravenous and oral use alike and is 30.0 and 36.0%, respectively.

APPLICATION OF INTRAVENOUS CHEMOTHERAPY AT THE INTENSIVE STAGE OF TREATMENT IN PATIENTS WITH PRIMARILY DIAGNOSED PULMONARY TUBERCULOSIS

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Background: Isoniazid, rifamycins, pyrazinamide, ethambutol and their combinations remain the main anti-tuberculosis drugs of today. The most active of rifamycins are synthetic derivatives – rifampicin and rifamycin sodium.

Methods: The study had a comparative clinical and pharmacological design. The study enrolled patients with primarily diagnosed pulmonary tuberculosis, distributed into homogenous main and control groups. The following therapeutic schedule was used: a total of 60 doses of isoniazid, rifamycin and ethambutol were administered via infusion as a part of 5-component therapeutic regimen with subsequent conversion of patients to standard therapy. Chromatographic method was used to determine serum concentrations of drugs. The study included 10 patients; each patient received a 600 mg single dose of the rifamycin intravenously. In several days the patients received the 600 mg of the reference drug rifampicin as a single oral dose.

Results: Intravenous administration of rifamycin was accompanied by higher serum concentrations of the drug than in oral administration of rifampicin. Decreased levels of rifamycin was observed already at the 1st hour of observation in 100% of cases; however, in course of the next 3 hours in 9 (90±9.5%) patients the concentrations of the drug were higher than the relevant indices in application of rifampicin. The maximal concentration of rifamycin after intravenous administration is 22.9 µg/ml on the average, which significantly exceeds the concentration produced by rifampicin – 8.9 µg/ml. Until the 5th hour of observation inclusive the concentrations of drugs found in blood of the patients were 20 times higher than the minimum inhibitory concentrations of rifamycin sodium and 9.7 times higher than those of rifampicin.

Application of the modified treatment scheme was accompanied by a trend towards more rapid (0.7 months faster) healing of decay cavities compared to standard therapy. According to the findings of smear microscopy, the patients with advanced pulmonary tuberculosis, when exposed to the modified treatment regimen, achieved sputum conversion 0.5 months faster.

Conclusion: Based on the results obtained, it was proved that treatment efficacy is increased in application of intravenous chemotherapy during the intensive phase of treatment in patients with primarily diagnosed pulmonary tuberculosis.

Abstract book of the 4th Conference of The Union Asia-Pacific Region 10-13 April 2013 (Ha Noi, Viet Nam)
THE SUBSTANTIATION OF INFUSION THERAPY WITH LEVOFLOXACIN IN PATIENTS WITH PRIMARILY DIAGNOSED PULMONARY TUBERCULOSIS WITH UNKNOWN SUSCEPTIBILITY OF THE CAUSATIVE AGENT TO ANTI-MYCOBACTERIAL AGENTS

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Introduction: The analysis of literature sources has indicated that in Ukraine the incidence of primary resistance of Mycobacteria tuberculosis (MBT) to anti-tuberculosis drugs (ATD) is from 7.0% to 20.0% depending on the geographical area; the overall secondary resistance is found in 75% of cases. In turn, multi-resistant tuberculosis (MRT) is detected in almost 9% patients with primarily diagnosed tuberculosis (PDTB) of the lungs, which is a very negative prognostic sign concerning the overall control of tuberculosis epidemics.

Further growth of primary and secondary resistance to chemotherapy results in prolongation of hospital stay, a substantial increase in financial expenditures for the treatment and increasing mortality rates, as well as insufficient scientific and theoretical base of preventing the selection of resistant strains in the patients requiring repeated treatment at high risk for multi-resistant tuberculosis.

The aim of the study: to substantiate the administration of Leflocin infusion therapy in patients with primarily diagnosed pulmonary tuberculosis in cases when causative agent’s profile of susceptibility to anti-mycobacterial drugs is unknown.

Methods: The object and methods of study: A total of 43 patients were enrolled in the study, of which 27 subjects with PDTB were at high risk for multi-resistance. Two groups were formed using simple sampling method, matching for age and the clinical forms of tuberculosis; male subjects predominated among the patients. Modern clinical, microbiological, immunological, laboratory/biochemical, radiological and statistical methods were used in course of the study.

Results: The analysis of study results has indicated that in empirical utilization of the schedules of anti-mycobacterial therapy suggested, which include Leflocin, sputum abacillation was observed in 84.6% of cases; partial resorption of focal and infiltrative lesions was observed in 76.9% cases; partial regression of caverns was found in 69.2% cases; improvement of clinical course – in 76.9% cases, whereas the intensive treatment phase employing standard regimens (Categories I and II) sputum abacillation was observed in 50% cases, partial resorption of focal and infiltrative lesions was found in 43.3% cases and partial regression of caverns was noted in 36.7% cases.

The advantage of the suggested method of differentiated pharmacological therapy is the step-wise and differentiated approach to administration of anti-mycobacterial therapy in patients at risk for multi-resistant...
tuberculosis (Category IV, The Order of the Ministry of Health of Ukraine No. 600 of 22.10.2008) with inclusion of highly effective drugs belonging to the family of 3d generation fluoroquinolones, which solves the problem of lack of time concerning the consequences of inducing resistance of Mycobacteria tuberculosis to a large quantity of AMBD in utilization of long-term (2-4 months since the initial patient assessment) routine test for drug susceptibility by inoculation to Lowenstein-Jensen selective medium.

1. Utilisation of the empirical regimen of the anti-mycobacterial therapeutic schedules suggested (with inclusion of Leflocin to the program) in patients with PDTB at risk for multi-resistance has produced significant results as compared with control group, namely: better sputum abacillation (in 84.6% vs. 50% cases), partial resorption of focal and infiltrative lesions (76.9% vs. 43.3% cases) and partial regression of caverns (69.2% vs. 36.7% cases).

2. Improvement of clinical course in utilization of intravenous Leflocin at the dose of 1.0 g for 1 month was registered in 78.7% patients of the main group.

Conclusion: Ukrainian Journal of Haematology and Blood Transfusion – No. 4d (15) – 2012
SECONDARY DRUG RESISTANCE DURING AN INTRAVENOUS INTERMITTENT CHEMOTHERAPY IN NEWLY DIAGNOSED CASES OF TUBERCULOSIS

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The purpose: To study frequency secondary drug resistance M. tuberculosis (SDR) during an intravenous (IV) intermittent chemotherapy in newly cases TB.

Methods: 76 pulmonary TB patients without previous chemotherapy enrolled in study. IV intermittent chemotherapy (3 times a week) appointed to 38 patients (IIC-group): isoniazid (H) and rifampicin (R) – 10 mg/kg IV, streptomycin (S) – 16 mg/kg intramuscularly (IM), pyrazinamide (Z) – 25 mg/kg per os. 38 patients received daily same doses of H, R, Z per os and S IM (a group of comparison).

Both groups were identical. We determined SDR initially and every 2 month of patient treatment during 5-14 months.

Results: Initially there were 16 patients IIC-group and 11 in a comparison group with fully sensitive TB. In IIC-group there were 6 patients with primary MDR and 16 with primary drug resistance (not the combination of H&R). In comparison group there were 4 patients with primary MDR, and 23 with primary drug resistance.

During chemotherapy 36 patients IIC-group and 34 from comparison group became sputum negative after 3,17±0,4 and 2,7±0,5 months accordingly (p=0,17, Mann-Whitney U-test). During the IV intermittent chemotherapy SDR appeared at 5 patients, secondary MDR – at 1 from 5. In comparison group SDR appeared at 4 patients, secondary MDR at 3 from 4 (RR=1,54, 95%CI: 1,34-1,75). The mean term of formation SDR appeared in 3±0,3 and 2±0 months accordingly (p= 0,03, Mann-Whitney U-test).

Conclusion: The occurrence risk of secondary MDR is lowered, SDR term is slower in IIC-group than in group of daily treatment, in about 3 months from the start of chemotherapy. This term coincides with sputum negative results at patients of both groups.

Abstract book of the 21st ERS Congress (24-28 September 2012, Amsterdam, Netherlands)
CLINICAL EFFICACY OF THE MODIFIED TREATMENT SCHEME IN PATIENTS WITH NEWLY DIAGNOSED PULMONARY TUBERCULOSIS

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State Institution “National Institute of Phthisiology and Pulmonology named after F.G. Yanovsky of the Academy of Medical Science of Ukraine”

The main reasons of treatment failures within the first 2-3 months (intensive treatment stage) include: failure to comply with treatment regimens, concomitant diseases, preventing the use of appropriate chemotherapy, drug resistance, the inability to reach the optimal concentrations of drugs in blood and tissues due to their poor absorption in the gastrointestinal tract or rapid inactivation of drugs. The objective of the work was to assess the efficacy of the modified treatment regimen with isoniazid, rifamycin (Rifonat®, 30mg/ml concentrate for infusion solution, produced by Yuria-Pharm Ltd., Ukraine) and ethambutol (Inbutol®, 10% injection solution, produced by Yuria-Pharm Ltd., Ukraine) by intravenous infusion.

The study involved 50 patients who were divided into the main group (MG) and control group (CG) (25 patients per group). All patients had newly diagnosed pulmonary tuberculosis. The difference between the main and control groups was the use of isoniazid, rifamycin (Rifonat®) and ethambutol (Inbutol®) by intravenous infusion as a part of the standard treatment in the main group, together with the intramuscular administration of streptomycin and oral administration of pyrazinamide. All these drugs were used in the permissible doses according to the pharmacopoeia requirements. Antibacterial therapy was assigned according to the category of follow-up care with subsequent correction after evaluation of Mycobacterium tuberculosis sensitivity.

By the end of the 2nd month of treatment, radiological positive dynamics (improvement) was observed in all 25 patients (100%) in the main group and in 18 patients (72.0%) in the control group (the signs of positive dynamics included: total or partial resolution of focal infiltrative changes, tuberculous cavity closures or reduction of their sizes. The average healing time of the cavitations in the main group was (3.0±0.2) months; and it was (3.9±0.3) months in the control group (p<0.05).

Summarizing the results of the clinical study, it has been found that the use of the modified treatment regimen using intravenous infusions of isoniazid, rifamycin (Rifonat®, 30 mg/ml concentrate for infusion solution, Yuria-Pharm Ltd., Ukraine) and ethambutol (Inbutol®, 10% injection solution, produced by Yuria-Pharm Ltd., Ukraine) as a part of etiotropic treatment has an advantage over the use of standard chemotherapy due to reducing the time to bacterioexcretion cessation and healing of tuberculous cavities, which makes it possible to recommend this method for the treatment of patients with newly diagnosed pulmonary tuberculosis.

Proceedings of the 5th International Scientific and Practical Conference on Tuberculosis and Lung Diseases, October 20-22, 2011, Baku, the Azerbaijan Republic
SERUM CONCENTRATIONS OF RIFAMPIN, ISONIAZID, AND INTESTINAL ABSORPTION, PERMEABILITY IN PATIENTS WITH MULTIDRUG RESISTANT TUBERCULOSIS

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Abstract

This study evaluates the serum concentrations of rifampin (RMP), isoniazid (INH), and intestinal barrier function in patients with multidrug-resistant tuberculosis (MDR-TB), drug susceptible tuberculosis (DS-TB), and health volunteers (HC; controls).

Peak serum concentrations of RMP were significantly lower in MDR-TB and DS-TB as compared with HC (odds ratio [OR]=3.125, confidence interval [CI] [1.037-9.418] and OR=4.025, CI [1.207-13.418], respectively). The INH peak serum concentration was not significantly different between MDR-TB versus DS-TB or DS-TB versus HC. The percent of mannitol excretion was significantly lower in the MDR-TB group compared with DS-TB (13.18 versus 16.03, analysis of covariance [ANCOVA], P=0.0369) and compared with HC (13.18 versus 16.61, ANCOVA, P=0.0291) the other study groups.

These data suggested a lower peak serum concentration of RMP for both MDR-TB and DS-TB as compared with the HC group. The data also showed a lower intestinal area of absorption in patients with tuberculosis and even worse in MDR-TB.

Low antimycobacterial drug concentrations have been observed in tuberculosis (TB) patients under treatment. The lactulose/mannitol urinary excretion test (L/M), normally used to measure intestinal permeability, may be useful to assess drug absorption.

The objective of this research was to study intestinal absorptive function and bioavailability of rifampin and isoniazid in TB patients. A cross-sectional study was done with 41 patients and 28 healthy controls, using the L/M test. The bioavailabilities of rifampin (R) and isoniazid (H) were evaluated in 18 patients receiving full doses. Urinary excretion of mannitol and lactulose, measured by HPLC, was significantly lower in TB patients. The serum concentrations of the drugs were below the expected range for R (8-24 mcg/mL) or H (3-6 mcg/mL) in 16/18 patients. Analyzing the drugs individually, 12/18 patients had low serum concentrations of R, 13/18 for H and 8/18 for both drugs.

We suggest that there is a decrease in the functional absorptive area of the intestine in TB patients, which would explain the reduced serum concentrations of antituberculosis drugs. There is a need for new approaches to improve drug bioavailability in TB patients.

The Brazilian Journal of Infectious Diseases 2006; 10 (December)
AN INTERMITTENT INTRAVENOUS CHEMOTHERAPY AT PATIENTS WITH PULMONARY TUBERCULOSIS AND VIRAL HEPATITIS B AND C

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The purpose: To compare the efficiency and tolerability of intermittent intravenous to daily traditional treatment in 2 groups patients with pulmonary tuberculosis (TB) and viral hepatitis comorbidity.

Methods: We have completed a randomized comparative prospective study of daily vs. intravenous intermittent chemotherapy for cases with TB and viral hepatitis. We have identified 129 patients with TB and chronic hepatitis B and C, which were randomized into 2 groups: #1 – 38 people – received standard chemotherapy every day; #2 – 91 people – received two times a week intravenously isoniazid 12 mg/kg, rifampicin 7.5 – 10 mg/kg, intramuscular – streptomycin 16 mg/kg, per os – pyrazinamide 25 mg/kg. These groups were identical.

Results: Cavity closure was diagnosed in 81.6% of patients #1 group, and in 94.5% cases of the group #2 (p<0.05), smear conversion to negative was observed in 89.5% (group #1) and in 96.7% (group #2) (p>0.05), accordingly. Toxic reactions occurred in 15 and 19 patients each corresponding group (p<0.05). We found that treatment outcomes of pulmonary tuberculosis in patients with adverse effects of chemotherapy was worse than in patients with good tolerance to medications (p=0.04). The occurrence risk of secondary multi-drug resistance is lowered to a more significant extent in #2 group than in #1.

Conclusion: Intermittent intravenous chemotherapy of patients with pulmonary tuberculosis and chronic viral hepatitis B and C comorbidity has the following advantages: a) it is highly efficient; b) it prevents the occurrence of toxic reactions (R=4.3, 95% CI 1.8-10.5), c) there is lower rate of development of secondary drug resistance (R=1.54, CI 95%: 1.34-1.75).
EFFICACY OF RHEOSORBILACT IN TREATMENT OF ACUTE SENSORINEURAL HEARING LOSS IN PATIENTS WITH LUNG TUBERCULOSIS DURING PHASE OF INTENSIVE CHEMOTHERAPY BY DATA TECHNICAL CONTROLS

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Background: Acute sensorineural hearing loss is one of the most frequent adverse reactions to anti-mycobacterial therapy in patients with pulmonary tuberculosis, which occurs mainly during first weeks of chemotherapy intensive phase. Rheosorbilact is a complex infusion product containing sodium lactate (1.9%), 6-carbon alcohol sorbitol (6%) and complex of electrolytes. Total osmolality of Rheosorbilact is three times higher than plasma osmolality and due to that fact the drag increases osmotic pressure of plasma and provides fluid moving from intercellular sector intravascularly with increasing of tissue perfusion and creating conditions for diffusion toxic factors from infected cells to the general circulation. The aim of the research was to learn Rheosorbilact effectiveness in the treatment of acute sensorineural hearing loss in patients with pulmonary tuberculosis during the intensive phase of antituberculosis chemotherapy according to the data of technical devices.

Methods: Into the study were included 30 patients with pulmonary tuberculosis who were affected with acute sensorineural hearing loss during the intensive phase of antituberculosis chemotherapy. The first group included 15 patients who received standard therapy of neuritis (vitamins Bl, B6 in a dose of 2 ml intramuscularly every other day, calcium pantothenate in a dose of 0.2-0.4 g 2 times a day, adenosine triphosphate in dose of 1.0 intramuscularly) in addition to intensive antituberculosis chemotherapy. Patients of the second group (15 persons) additionally used Rheosorbilact intravenously in a dose of 200 mg/day according described scheme during entire intensive phase of antituberculosis chemotherapy. Vascular drugs were not administered.

Results: In patients of the 1st group positive dynamics of clinical symptoms was not noted or observed even their deterioration. Thus, in 4 patients of this group indicators were unchanged, in 8 was diagnosed moderate and in 3 cases – significant hearing loss and that was confirmed with data of audiometry in the late phase of intensive chemotherapy. The earliest clinical effect was noted in patients of the 2nd group at 8-10 days of treatment decreased ear noise, headache, there was a slight improvement in clarity of language, normalization of sleeping. Were determined reducing the intensity of symptoms of labyrinth disorders and was present stabilization of audiometric indicators in the late phase of intensive chemotherapy.

Conclusion: Usage of the Rheosorbilact in the treatment of acute sensorineural hearing loss in patients with pulmonary tuberculosis during the intensive phase of antituberculosis chemotherapy lead to reducing symptoms of drug intoxication and improving blood rheology and that manifested in positive dynamics of clinical symptoms, reducing ear noise, stabilization of audiogram indexes, normalization of the vestibular apparatus.

Certainly, etiotropic treatment is the main one in the treatment of tuberculosis, but it is known that with the help of the pathogenetic mechanisms of influencing the course of the disease may be improved the efficiency of the disease treatment. One of such mechanism is the improvement of rheological properties of blood, in particular – reducing its viscosity. Our attention was drawn by Rheosorbilact (major pharmacologically active ingredients of the drug are sorbitol and sodium lactate and also electrolytes Ma⁺, Ca²⁺, K⁺, Na⁺ and Cl⁻). The aim of our research was to study the influence of Rheosorbilact on blood viscosity in patients with newly diagnosed pulmonary tuberculosis.

For solving objectives we formed two groups of patients: the 1st (control) group included 102 patients and the 2nd (research) – 106. Patients of both groups were sick with newly diagnosed destructive pulmonary tuberculosis with bacteria expulsion, established by microscopy. Patients in both groups belong to the 1st category. By age and sex composition, clinical forms, prevalence of the pathological process, comorbidities, and blood viscosity before treatment both study groups were no statistically different (p>0.05). All patients were prescribed standard five component scheme of anti-tuberculosis therapy (isoniazid, rifampicin, pyrazinamide, ethambutol and streptomycin) in doses which were adequate to their weight. Patients of the first group additionally were administered of intravenous infusion of 400 ml of 5% glucose solution, and patients of the second group – 400 ml of Rheosorbilact (every other day, starting from the second day of antimycobacterial therapy, consisting of 10 infusions). Other drugs, nutritional supplements and physical therapy for patients of both groups were not prescribed. In all patients blood viscosity was measured by a viscometer, the day before infusion of Rheosorbilact or 5% glucose solution and after 5 days of their completion (normal – 0,0043-0,0054 n*s/m²).

Before treatment blood viscosity was significantly increased in all patients of both groups ((0,0089±0,0010) n*s/m² in the 1st group and (0,0088±0,0009) n*s/m² in the 2nd group). Control measurement of blood viscosity in patients of the 1st group did not shown significant changes ((0,0087±0,0008) n*s/m², p>0.05), and in patients of the 2nd group it was significantly decreased and was within normal ranges ((0,0050±0,0007) n*s/m², p<0.05).

Consequently, results of the study suggested that Rheosorbilact combined with specific therapy reduces blood viscosity in patients with newly diagnosed destructive pulmonary tuberculosis. Therefore, we can assume that this drug may improve the effectiveness of treatment of these patients. This assumption requires further study and may be the subject of a number of scientific researches.
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