



Optimal Combination of Doses for Isoniazid and Vitamin B₆ to Treat Tuberculosis Destructive Guinea Pigs

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Abstract: This paper presents the results of morphological studies of tuberculosis and nonspecific inflammatory changes of the guinea pigs in the treatment of different ratios of isoniazid with pyridoxine hydrochloride. The optimal dose ratio of the expression of specific and non-specific manifestations of inflammation in the lungs, liver, kidneys and spleen. Also prayed to interpret the results of studies for the treatment of destructive tuberculosis in humans. It was proposed a method of determining the optimum ratio of doses of the most pronounced therapeutic effect and minimal side effects. The aim of the study was to conduct morphological evaluation of lesions of internal organs (lungs, liver, kidneys, spleen) after treatment of experimental tuberculosis of guinea pigs different ratios of doses of isoniazid and pyridoxine hydrochloride. The optimal therapeutic effect is obtained by treating animals with experimental tuberculosis isoniazid at a dose of 26 mg/kg of vitamin B₆ and 10mg/kg body weight of the animal, thus completely disappeared phenomenon specific inflammation in the lungs, liver, kidneys and spleen. This phenomenon also disappeared perifocal nonspecific inflammation. Disappeared dystrophic and necrotic changes in the studied organs.

Keywords: Tuberculosis, Experimental Model, Guinea Pigs, Isoniazid, Vitamin B₆, Optimal Ratio

1. Introduction

The situation on tuberculosis (TB) in Ukraine is quite complicated. Tuberculosis is not only a medical problem. This social problem, which reflects the socio-economic situation, cultural, educational and welfare level, the degree of health care, including TB services. And this disease in recent years causing great concern in Ukraine and the Ministry of Health of Ukraine in particular. [1] However, TB is now a national danger for Ukraine as a reservoir of TB infection. Tuberculosis causes significant economic damage and the later it is diagnosed, the more spread than later started fighting with him, the harder it is to eliminate the more need to spend for this, and the greater the economic damage. [2] Therefore, research in the field of TB control are extremely important nowadays.

This study has general biological and social importance of protecting people from tuberculosis, which is transmitted to

people from both people with TB. [3, 4] The study used a combination of mathematical and experimental models allows to solve two problems at once: defining features of the treatment of tuberculosis in guinea pigs and the possibility of interpretation of the data on the human body.

Using an guinea pigs experimental model of destructive tuberculosis enables decide on the optimal ratio of doses of isoniazid and pyridoxine hydrochloride to prevent the occurrence of side effects tuberculosis is highly contagious guinea pigs to humans and is very resistant to various environmental changes. [3]

Guinea pigs are well suited to study airborne TB transmission due to their exceptional vulnerability to infection with as little as a few inhaled mycobacteria. [5] The guinea pig also replicates many aspects of TB infection in humans, including the formation of granulomata, primary and hematogenous pulmonary lesions, dissemination, and caseation necrosis. [6, 7]

2. Methodology

For the experiment, 50 guinea pigs have an average weight of 250 g was formed nine groups of animals to 5 animals in each group with different chemotherapy regimens experimental tuberculosis caused by *Mycobacterium tuberculosis* subcutaneous laboratory strain H₃₇Rv at a dose of 0.01 mg wet weight to volume 0,5 ml physiological

sodium chloride solution. After 1.5 months one of the pigs hammer in to control the state of tuberculosis caused by mycobacteria inoculation. Defeat assessed in conventional indices of infestation (if Drabkin RO), which most pronounced macroscopic lesions take 100 conventional units. Slaughtered pigs to control the index is in the range of 90-100 conventional units (c.u.).

3. Results and Discussion

Table 1. Results of treatment of experimental tuberculosis of guinea pigs isoniazid and vitamin B₆ (isoniazid per os, pyridoxine hydrochloride subcutaneously).

№ Group	Doses of drugs, mg / kg		The indices of infestation of each pig				Average Index defeats (c.u.).
	Isoniazid	Vitamin B ₆	lung tissue	liver tissue	kidney tissues	spleen	
1	10	0	25	29	22	25	27,2
2	32	0	25	38	27	31	31,4
3	100	0	35	39	34	36	35,4
4	10	5	22	19	24	35	23,8
5	10	50	23	17	10	7	15,2
6	32	5	7	16	9	13	12,4
7	32	50	32	20	22	26	24,4
8	100	5	17	7	24	19	15,6
9	100	50	38	16	7	20	17,6
10	0	0	90	100	100	100	98,0

As can be seen from the data in Table 1, with a steady dose of isoniazid 10 mg / kg, the growth of vitamin B₆ in the range of its doses of 0 mg / kg, 5 mg / kg, 50 mg / kg leads to a constant decrease in the mean index of infectiousness of 27.2%; 23.8% and 15.2% respectively. At the same time, with a steady dose of isoniazid 32 mg / kg, the abovementioned doses of vitamin B₆ (0 mg / kg, 5 mg / kg, 50 mg / kg) are more complex. At first, the average index of lesions drops sharply from 31.4% to 12.4%, and then at a dose of vitamin 50 mg / kg again increases rapidly and makes 24.4%. A similar dependence is also observed at a steady dose of isoniazid in 100 mg / kg. Under the influence of doses of vitamin B₆ (0 mg / kg, 5 mg / kg, 50 mg / kg), the

average index of lesions of guinea pigs also initially falls from 35.4% to 15.6%, and then slightly increases to 17.6%. Such results demonstrate the complexity of the dependence the process of treatment of destructive tuberculosis of guinea pigs on the dose of therapeutic agents - isoniazid and vitamin B₆. In general, the lowest average index of organ damage 12.4 c.u. was obtained in the treatment of destructive tuberculosis of guinea pigs with isoniazid in a dose of 32 mg / kg with vitamin B₆ in a dose of 5 mg / kg. A close to this result is the magnitude of the average index of damage of 15.2 c.u. received in the chemotherapy regimen, which included isoniazid in a dose of 10 mg / kg and vitamin B₆ in a dose of 50 mg / kg.

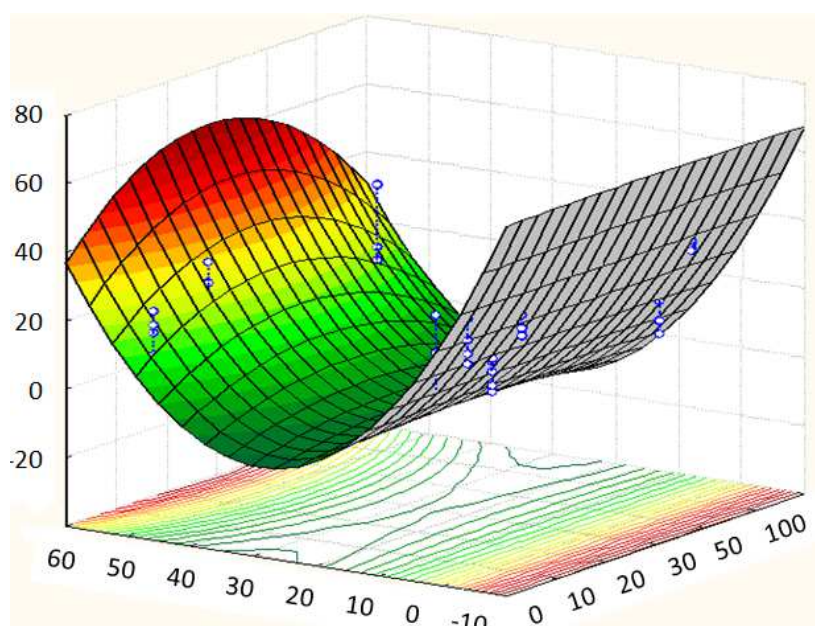


Figure 1. Mathematical processing results of treatment of experimental tuberculosis of guinea pigs isoniazid and vitamin B₆.

Mathematical processing shows that the therapeutic dose of isoniazid almost optimal (10 mg / kg) a further increase does not lead to a therapeutic effect and dose vitamin B₆ significantly reduced. It suggest using isoniazid 10 mg / kg in combination with a dose of pyridoxine hydrochloride 26 mg / kg.

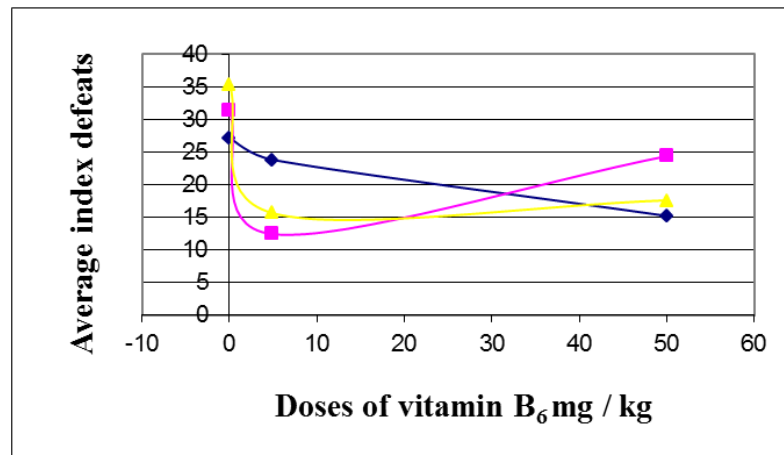


Figure 2. The dependence of the average lesion index guinea pigs doses of vitamin B₆ on a constant dose of isoniazid.

- 1 - \diamond at a dose of isoniazid 10 mg / kg;
 2 - \square at a dose of isoniazid 32 mg / kg;
 3 - Δ at a dose of isoniazid 100 mg / kg;

Table 2. Changes in tissues of animals treated with isoniazid 32 mg / kg body weight of vitamin B₆ 5 mg / kg.

<p>Changes in lung tissue Very minor changes to lung tissue, determined by small areas of infiltration (1). No specific inflammatory response. Blood supply capillary membranes interalveolar moderate (2).</p>	<p>Changes in liver tissue The structure of the liver is preserved. Degenerative changes were not found. No inflammatory and necrotic changes.</p>
<p>Changes in kidney tissues The structure of the kidney without substantial changes. Moderate kidney tissue blood supply. Cavities capsules kidney cells is not extended. No inflammatory and necrotic changes</p>	<p>Changes in the tissues of the spleen The structure of the spleen retained. Moderate blood supply tissue spleen. No inflammatory and necrotic changes.</p>

The optimal therapeutic effect was obtained in the treatment of animals with experimental tuberculosis in a dose of isoniazid 32 mg / kg and vitamin B₆ at a dose of 5 mg / kg body weight, while the phenomena of specific inflammation in the lungs, liver, kidneys and spleen completely

disappeared. At the same time, the phenomenon of perifocal non-specific inflammatory process disappeared.

In the experiment Shuttle "INH – pyridoxine hydrochloride" 32 and 5 mg/kg respectively leads to a lack of specific and non-specific manifestations of inflammation in

the lungs, liver, kidneys and spleen.

Last decade findings of high-dose isoniazid use potential effectiveness for isoniazid-resistant strains bearing *inh A* mutation lead to WHO recommendation to include this drug into the second-line treatment regimen for multidrug resistant TB (MDRTB). Unlike sensitive TB treatment this regimen takes 9-20 months. Pyridoxine deficiency is also due to cycloserine, another drug for MDR TB treatment. [8] This inevitably increases the rate of peripheral neuropathy and other manifestation of pyridoxine-deficiency in TB patients. At the same time, the dosage of pyridoxine supplementation is not elaborated for different clinical situations and isoniazid dosage. The existing recommendations are dated at 80s or earlier, are related to the dosage up to 15,6 mg/kg, and do not contain the experimental evidence of the dosage. At the same time, currently the dosage of 16-18 mg/kg is used and pyridoxine dosage is titrated based on neuropathy clinical response only [9, 10].

Therefore, given the growing burden TB and MDRTB the detailed evidence-base dosage instructions are of the urgent need. The controlled clinical trial (Phase II) is aimed at clarifying the optimal pyridoxine doses in dependence of the isoniazid and cycloserine dosage. Current clinical recommendation suggests to use pyridoxine in the dose of 100-200 mg per day, whereas dosage of 25 mg/kg per day is proven to be well-tolerated and does not exceed the allowed maximum. Previous study on the animal model demonstrated the minimal rate of tissue lesions at this pyridoxine dosage. Therefore the study anticipates comparison of the clinical effects of these doses with the conventional dosage of 100-200 mg per day. Taking into consideration the deference of isoniazid toxicity in slow and rapid isoniazid inactivator phenotypes the trial may include two arms rolling-in each phenotype.

4. Conclusion

The use of an experimental model of destructive tuberculosis makes it possible to decide on the optimal dose ratio of isoniazid and pyridoxine hydrochloride to prevent side effects.

It is proved that the effectiveness of treatment of patients with destructive tuberculosis, when they are affected by the strain of mycobacterium tuberculosis H₃₇Rv, is directly proportional to the use of the optimal dose ratio of isoniazid and vitamin B₆ (10 and 26 mg / kg, respectively).

The mathematical dependence between the index of organ damage after treatment with isoniazid and vitamin B₆ is proposed and the index of organ affliction in the selected range is almost independent of the concentration of isoniazid. The clinic's dose of isoniazid is almost optimal (10 mg / kg), and the dose of vitamin B₆ requires an increase of almost 5 times to a value of 26 mg / kg.

This approach, which indicates corrected ratios of isoniazid and vitamin B₆ formulations in the treatment regimen, can be expected to improve the treatment outcome,

depending on the specificity of the body's tuberculosis in general and each organ in particular.

Further experimental and clinical studies on this issue will not only specify the purpose of these drugs, but also create new schemes for the practical application of them as a means of modern medical science.

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Biography



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