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Abstract

Full Text

Chemistry

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Tuberculostatic Properties of the Mixed Thiosemicarbazone Guanilhydrazone of Indandione-1,3—a Representative of a New Type of Antituberculosis Agents

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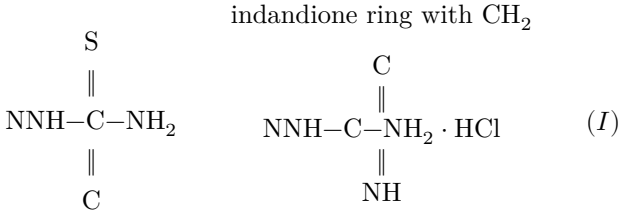
The development of drug resistance of microbes to antibiotics and chemotherapeutic agents justifies research aimed at finding new antibacterial preparations that act on resistant forms of microorganisms.

In studying a little-investigated type of tuberculostatic substances—β-diketones—it was found that some guanilhydrazones and mixed thiosemicarbazone guanilhydrazones of β-diketones recently synthesized by us ([1,2]) *in vitro* exhibit rather high bacteriostatic activity also against strains of tuberculous mycobacteria resistant to preparations of isonicotinic acid hydrazide and streptomycin. This bacteriostatic action is also manifested in an *in vivo* experiment ([3]). The most promising of them—thiogin (I)—was subjected to more detailed study. Thiogin is the hydrochloride salt of the thiosemicarbazone guanilhydrazone of indandione-1,3.



(*I*)

Thiogin is a mustard-yellow crystalline powder, of bitter taste, with a melting point of 225-226° (with decomposition); it dissolves in water in a ratio of 1 : 330, is poorly soluble in alcohols, and is insoluble in ether and benzene. Thiogin is a preparation of a new combined type, containing elements of four tuberculostatically active atomic groupings: thiosemicarbazide, guanidine, hydrazine, and β-diketone groupings.

The experimental study of thiogin was carried out by the staffs of the Department of Experimental Chemotherapy and Pharmacology of the Institute of Organic Synthesis and the Tuberculosis Sector of the Institute of Experimental Medicine of the Academy of Sciences of the Latvian SSR.

In *in vitro* and *in vivo* experiments, thiogin exerts a specific, pronounced bacteriostatic effect only with respect to tuberculous myco-

bacteria of the human and bovine types. Tuberculous mycobacteria were cultured on modified Model semiliquid media, pH 7.0, at a temperature of 37°, for 30 days. Serial dilution methods were used to determine the tuberculostatic titer. The tuberculostatic action of the preparation on sensitive strains of tuberculous mycobacteria in vitro is manifested at dilutions of 1:200,000–1:500,000, and on strains resistant to streptomycin and tubazid at dilutions of 1:125,000–1:130,000. It was found that thiogin inhibits the catalase activity of tuberculous mycobacteria. A delay in the intensity of respiration was also observed.

Thiogin in daily doses of 25–100 mg/kg gives a good therapeutic effect in experimental tuberculosis of guinea pigs infected with strains of tuberculous mycobacteria sensitive to streptomycin and tubazid (Table 1), and in doses of 50–100 mg/kg–in guinea pigs infected with the resistant strain "Fe," isolated from a patient with tuberculosis. The mentioned resistant strain grows even in media containing streptomycin or phthivazid at a dilution of 1:10,000. Thiogin gives an especially good therapeutic effect in experimental tuberculosis of guinea pigs at doses of 100 mg/kg. Bacterioscopic and bacteriological studies of the organs of treated guinea pigs also indicate the high antituberculous activity of thiogin.

Table 1

Index of tuberculous involvement in experimental guinea pigs infected with the sensitive "Ravenel" strain of tuberculous mycobacteria and the resistant "Fe" strain (according to the 21-point system)

Strain "Ravenel"	Index	Strain "Fe"	Index
Thiogin		**Thiogin**	
Group I. 25 mg/kg, per os	6.5	Group I. 50 mg/kg, per os	3.1
II. 50 » » »	4.0	II. 100 » » »	2.4
III. 100 » » »	2.0	**Control**	
IV. 10 » intramuscularly	4.4	Group III. Did not receive the preparation	7.9
Control			
Group V. Did not receive the preparation	17.6		

The acute toxicity of thiogin when administered intraperitoneally to white mice is 310 mg/kg (248–387 mg/kg), while with a single oral administration to white mice in doses from 500 mg/kg to 10,000 mg/kg no toxic phenomena were observed. In determining the chronic toxicity of thiogin in dogs at doses of 100 mg/kg, no pathological changes in the function of parenchymatous organs could be detected, except for dyspeptic phenomena (liquid stool, vomiting) at the beginning of the experiment, which gradually disappeared.

In the organism of growing white rats and guinea pigs, thiogin, even in doses up to 100 mg/kg, produced no side effects, and in the liver of these groups of rats no substantial deviation from the norm was observed on chemical and histological examination. Studies of the content of thiogin in the organs of guinea pigs and white rats were carried out according to a slightly modified Jacob method, used for determining isonicotinic acid hydrazide. The results are given in Table 2.

It is especially interesting and important that, of all the internal organs of guinea pigs, the highest concentration of thiogin was noted in the lung tissues (1.05 mg%), while in the liver it was lower (0.74 mg%). An entirely different picture was observed in the treatment of experimental tuberculosis with tubazid or phthivazid. In the lung tissues of guinea pigs, the concentration of isonicotinic acid hydrazide averaged, respectively, 0.55 or 0.51 mg%,

and in the liver, 1.25 or 1.23–2.5 mg%. This is of great importance, since greater accumulation of isonicotinic acid hydrazide in the liver and less in the lungs may play a certain role in the development of disturbances of liver function, as well as in the efficacy of treatment of pulmonary tuberculosis.

Also of interest is the fact that in guinea pigs a high concentration of thiogin was achieved in brain tissue–0.60 mg% (with tubazid and phthivazid only 0.04-0.09 mg%).

Table 2

Concentration (mg%) of the drug thiogin in the blood and internal organs of experimental animals after daily oral administration of thiogin

	Guinea pigs(20 mg/kg per day for 10 days)	Rats (25 mg/kgper day for 84 days)
Blood	0.25	–
Lungs	1.05	0.83
Liver	0.74	0.52
Spleen	0.65	0.69
Kidneys	–	0.80
Brain	0.60	0.47
Stomach wall	1.30	–
Intestinal wall	1.65	–

Thiogin, administered *per os*, was rapidly detected in blood serum and urine. Its maximum concentration was determined approximately 4–6 hours after administration. According to the above-mentioned indices, thiogin is not inferior to, and by some measures even exceeds, the indices of the well-known foreign antituberculosis drug—the thioamide of α-ethylisonicotinic acid (ethionamide, preparation 1314) (4).

The experimental data obtained make it possible to recommend thiogin for clinical testing in the treatment of patients with tuberculosis with mycobacteria resistant to generally known chemotherapeutic agents.

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Note: Figure translations are in progress. See original paper for figures.