THE USE OF A NEW ANTITUBERCULOSIS DRUG – THIANIDE (1314 Th) – IN CONJUNCTION WITH STREPTOMYCIN OR PHTHIVAZID

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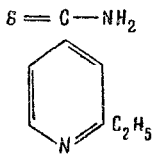
In 1958, N. F. Kucherova, R. M. Khomutov, E. I. Budovskii and others [1], working in the division of organic synthesis of the Institute of Pharmacology and Chemotherapy of the AMN SSSR, used an original method to synthesize a new antituberculosis preparation thianide, the thioamide of α-ethylisonicotinic acid. The analogous compound was obtained in 1957 in France by Riste and called 1314 Th. Its empirical formula is $C_8H_{10}N_2S$, and its structural formula:



We studied thianide in experiments in vitro. These showed that the compound possesses a bacteriostatic action on various species of Mycobacterium tuberculosis, both sensitive and resistant to other chemotherapeutic agents. Trials of thianide in the treatment of hematogenous tuberculosis in white mice and tuberculosis in guinea pigs showed it to be highly effective.

As a result of our experimental investigations, the Pharmacological Committee recommended clinical trials of thianide. Prolonged treatment of patients with a single antituberculosis drug may lead to the appearance of resistant strains of M. tuberculosis in these patients. We therefore carried out experiments on animals in which thianide was used in conjunction with streptomycin and phthivazid.

EXPERIMENTAL METHOD

The chemotherapeutic activity of the compounds when administered together was studied in experimental hematogenous tuberculosis in white mice. Mice weighing 18-20 g were used in the experiment. The animals were inoculated intravenously. In some experiments the strain B bovinus 8 (bovine type) was used in a dose of 0.1 mg for each mouse, and in others a virulent strain of human type $H_{37}Rv$ in a dose of 0.05 mg for each mouse.

Treatment began on the day after inoculation. The control group and each experimental results were assessed in accordance with the macroscopic changes, the weight of the lungs, and the number of tubercle bacilli in films of the lungs. These changes were recorded by means of a 3-point system as suggested by M. V. Trius. The animals were sacrificed when 70% of the control mice had died.

EXPERIMENTAL RESULTS

In Tables 1 and 2 we show the mean indices of the chemotherapeutic efficacy of thianide, of streptomycin, and of the two together. Thianide was given by mouth and streptomycin intramuscularly.

It will be seen from Table 1 that the most effective treatment resulted from a combination of thianide in a dose of 0.65 mg with streptomycin in a dose of 400 units. When this combination was used, the index of the macroscopic changes in the lungs was low, the weight of the lungs was the same as that of healthy animals, and no tubercle bacilli were seen in the lung films.

TABLE 1. Chemotherapeutic Efficacy of Thianide, Streptomycin, and a Combination of Both in Animals Inoculated with the Bovine Strain B. bovinus 8

Group	Preparation	Daily dose of preparation per mouse	Mean index of macroscopic changes in lungs	Mean weight of lungs (in mg)	Presence of M. tuberculosis in lung films
Control	–	–	2.54	620	+++
Experimental	Thianide	0.65 mg	1.35	270	+
"	–	1.3 mg	0.86	230	0
"	Streptomycin	200 units	1.6	295	+
"	"	400 units	0.9	265	0
"	Thianide + streptomycin	0.65 mg + 200 units	1.1	255	0
"	Ditto	0.65 mg + 400 units	0.3	218	0

TABLE 2. Chemotherapeutic Efficacy of Thianide, Streptomycin, and a Combination of Both in Animals Inoculated with the Human Strain $H_{37}Rv$

Group	Preparation	Daily dose of preparation per mouse	Mean index of macroscopic changes in lungs	Mean weight of lungs (in mg)	Presence of M. tuberculosis in lung films
Control	–	–	3	1014	+++
Experimental	Thianide	0.65 mg	2.83	727.2	++
"	"	1.3 mg	2.77	779.4	++
"	"	2.25 mg	1.6	298	0
"	Streptomycin	200 units	2.25	590.7	+
"	"	400 units	1.2	420	0
"	"	800 units	0.96	352	0
"	"	1600 units	0.82	318	0
"	Thianide + streptomycin	0.65 mg + 400 units	1.1	340	0
"	Ditto	1.3 mg + 400 units	0.93	325	0
"	"	1.3 mg + 800 units	0.53	260	0

The figures in Table 2 show that the human strain of M. tuberculosis $H_{37}Rv$ causes an infection in mice with a more severe course, as is apparent from all the chemotherapeutic indices. The mean weight of the lungs in the control animals was more than 1 g, the mean index of macroscopic changes in the lungs 3, and many mycobacteria were seen in lung films. Against the background of such a severe infection, a dose of 2.25 mg of thianide or of 800 and 1600 units of streptomycin failed to produce the usual effect. High indices of therapeutic efficacy were obtained only from the use of a combination of thianide in a dose of 1.3 mg with streptomycin in a dose of 800 units.

In Tables 3 and 4 we give the mean indices of chemotherapeutic efficacy of thianide and phthivazide, alone and in conjunction with each other. The compounds were administered by mouth.

It may be seen from Table 3 that indices of high therapeutic efficacy were observed after the combined administration of thianide in a dose of 0.65 mg and phthivazid in a dose of 0.4 mg. The figures in Table 4 show that

since the course of the infection after inoculation with strain $H_{37}Rv$ was severe, larger doses of the preparations were required for treatment. The most effective treatment resulted from a combination of thianide in a dose of 1.3 mg and phthivazid in a dose of 0.6 mg.

TABLE 3. Chemotherapeutic Activity of Thianide, Phthivazid, and a Combination of Both in Animals Inoculated with the Bovine Strain B. bovinus 8

Group	Preparation	Daily dose of preparation per mouse	Mean index of macroscopic changes in lungs	Mean weight of lungs (in mg)	Presence of M. tuberculosis in lung films
Control	–	–	2.54	620	+++
Experimental	Thianide	0.65	1.35	270	+
"	"	1.3	0.86	230	0
"	Phthivazid	0.25	0.96	286	±
"	"	0.4	0.64	252	0
"	Thianide + Phthivazid	0.65+ 0.25	0.86	256	0
"	Ditto	0.65+ +0.4	0.2	225	0

TABLE 4. Chemotherapeutic Efficacy of Thianide, Phthivazid, and a Combination of Both in Animals Inoculated with the Human Strain $H_{37}Rv$

Group	Preparation	Daily dose of preparation per mouse	Mean index of macroscopic changes in lungs	Mean weight of lungs (in mg)	Presence of M. tuberculosis in lung films
Control	–	–	3	1014	+++
Experimental	Thianide	0.65	2.83	727.2	++
"	"	1.3	2.77	779.4	++
"	"	225	1.6	298.0	0
"	Phthivazid	0.4	1.2	304.0	0
"	"	0.6	0.86	283.0	0
"	Thianide + Phthivazid	1.3+ 0.4	0.78	275.0	0
"	Ditto	1.3+ 0.6	0.44	225.0	0

These investigations showed that in mice infected with B. bovinus 8 (bovine type of M. tuberculosis) the administration of thianide in a dose of 0.65 mg had an inadequate therapeutic action. The same remarks apply to streptomycin in a dose of 400 units and phthivazid in a dose of 0.4 mg. The combined administration of thianide in a dose of 0.65 mg and streptomycin in a dose of 400 units to each mouse daily, or of thianide in a dose of 0.65 mg and phthivazid in a dose of 0.4 mg led to an increase in the therapeutic activity of both preparations and gave good results. In this way it was possible to reduce the daily therepeutic dose of thianide by two thirds and that of streptomycin by 67-71%.

When the animals were infected with M. tuberculosis strain $H_{37}Rv$ (human type), causing a severe hematogenous form of tuberculosis, thianide even in a dose of 2.25 mg daily to each mouse did not have an adequate therapeutic effect. The same remarks apply to streptomycin in a dose of 800 units and phthivazid in a dose of 0.6 mg. The combined administration of thianide in a dose of 1.3 mg and streptomycin in a dose of 800 units or of thianide in a dose of 1.3 mg and phthivazid in a dose of 0.6 mg daily to each mouse increased the chemotherapeutic action of both preparations. It follows that when animals are infected with the strain $H_{37}Rv$, the therapeutic doses of preparations must be increased.

These data may be caused when clinical trials of these preparations are made on patients with tuberculosis.

SUMMARY

Chemotherapeutic activity of thianide (1314 Th) in combination with streptomycin or phthivazid was studied on a model of hematogenic tuberculosis of white mice. In experimental infection of mice with mycobacteria B. bovinus 8 a daily dose of 0.65 mg per mouse of thianide alone proved to be therapeutically ineffective. Combined administration of thianide and streptomycin, or thianide and phthivazid led to potentiated chemotherapeutic activity of both preparations, giving a positive therapeutic effect. These data permit a three-fold reduction of the daily therapeutic dose of thianide and streptomycin. In infecting the animals with mycobacteria tuberculosis $H_{37}Rv$ (of the human type), causing severe hematogenic tuberculosis in mice, combined use of thianide (1.3 mg) and streptomycin (800 units), or thianide (of 1.3 mg) and phthivazid (0.6 mg) also led to intensified chemotherapeutic activity of both preparations. These preparations may be used in the treatment of tuberculosis in man.

LITERATURE CITED

1. N. F. Kucherova, R. M. Khomutov, E. I. Budovskii, et al., Zh. Obshchei Khimii (1959), No. 3, p. 915.
