REDUCING THE TOXICITY OF TUBAZID BY ADMINISTERING IT IN COMBINATION WITH CYCLOSERINE

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Tubazid (Isoniazid) is an effective antituberculotic preparation, large doses of which can have an unfavorable effect on the nervous system, causing excitation or drowsiness, vertigo, headaches, convulsions and even psychoses in patients [5,9,15]. Experimentally, large doses of Tubazid have induced convulsions in all sorts of laboratory animals [1,4].

A combination of Tubazid and cycloserine has been used recently to treat tuberculosis [6,11]. According to the data of Volinskii et al. [14], cycloserine enhances the therapeutic activity of Tubazid. It is interesting to note that, in a number of cases, cycloserine has a side effect similar to the effect of Tubazid [3,7,12,13]. Of course, the fact that Tubazid and cycloserine are used in smaller doses when administered in combination reduces the toxicity of each of these drugs. However, the literature data and our own investigations suggest that the reduced toxicity of Tubazid when used with cycloserine could be due to a possible antagonism of cycloserine to the toxic action of Tubazid, as well as to the reduction in the dose of the preparation. Prescott et al. [10], in experiments on white mice, established that cycloserine raises the tolerance dose of Tubazid. The authors used very large doses of cycloserine: 25-300 mg of the preparation per 20 g of weight, given internally. Monaco [8], who found some antagonism between cycloserine and Tubazid in an experiment on white mice, also used a very large dose of cycloserine: 300 mg/kg intraperitoneally. These authors used d-cycloserine in their experiments.

TABLE 1. Effect of d,l- and d-Cycloserine on the Toxicity of Tubazid to Mice

Dose (in mg/kg weight)	Tubazid		d,l-cycloserine + Tubazid		d-cycloserine + Tubazid	
	convulsant effect	lethal effect	convulsant effect	lethal effect	convulsant effect	lethal effect
100	0/10	0/10	0/10	0/10	0/10	0/10
125	6/4	1/9	1/9	0/10	4/6	1/9
150	7/3	5/5	3/7	1/9	5/5	2/8
175	9/1	7/3	2/8	0/10	10/0	7/3
200	10/0	7/3	6/4	4/6		8/2
225		6/4	9/1	8/2		10/0
250		9/1	10/0	10/0		
275		10/0				

Note: In the "convulsant effect" columns, the numerator is the number of mice in which convulsions developed, and the denominator is the number of mice which did not develop convulsions; in the "lethal effect" columns, the numerator is the number of mice that died, and the denominator is the number of mice that survived.

In collaboration with G. H. Kivman, we established the synergism of cycloserine with arecoline and nicotine in regard to tremor [2] and its antagonism to corasole [pentylenetetrazole] and strychnine with respect to the development time of convulsions; in the latter case, we established a quantitative difference between the effects of d,l-cycloserine and d-cycloserine [3].

METHODS

The experiments were performed on 300 white mice weighing 18-20 g. We determined the effect of preliminary cycloserine administration on the size of the 50% convulsant dose (CD_{50}) and the 50% lethal dose (LD_{50}) of Tubazid. We also established the time at which convulsions developed and the duration of the mice's life; d,l-cycloserine and d-cycloserine were given perorally in a dose of 50 mg/kg. Tubazid was administered intraperitoneally in doses starting at 100 mg/kg and increasing by 25 mg intervals up to 275 mg/kg. Ten mice were used for each dose. The convulsant effect of Tubazid became apparent 30-40 min after the administration of the drug. In this connection, cycloserine was administered $1\frac{1}{2}$ hrs before Tubazid so that a high concentration of both preparations would be found in the blood after 2 hrs.

TABLE 2. Effect of d,l- and d-Cycloserine on the Onset of Convulsions and the Life Span in Mice Given Tubazid

Number of animals	Dose (in mg/kg weight)	Tubazid				d,l-cycloserine + Tubazid				d-cycloserine + Tubazid			
		time convulsions developed (in min)	Sx^{-1}	life duration of mice (in min)	Sx^{-1}	time convulsions developed (in min)	Sx^{-1}	life duration of mice (in min)	Sx^{-1}	time convulsions developed (in min)	Sx^{-1}	life duration of mice (in min)	Sx^{-1}
10	125	62	1,4	115	One mouse died	114	Observations on one mouse	-[2]	-	69	2,7	113	One mouse died
10	150	63	2,2	103	20,5	100	11,3	147	One mouse died	62	5,6	110	16,0
10	175	55	6,6	74	14,2	92	2	-	-	54	4,2	71	4,0
10	200	49	4,9	72	5,9	83	8,3	105	12,7	54	5,1	77	10,4
10	225	42	8,1	71	4,5	73	8,6	96	5,4	46	2,3	80	7,2
10	250	44	4,9	67	6,6	69	4,4	88	4,4	41	4,0	67	4,7

[1] Sx^{-1} = standard error of arithmetic mean.

[2] — = none of the mice died.

RESULTS

The data on which we based our calculations of the CD_{50} and LD_{50} of Tubazid are shown in Table 1.

The Berens and Schlosser method was used to compute the CD_{50} and LD_{50} The CD_{50} of Tubazid was to be 159.2±8.36mg/kg. After preliminary d,l-cycloserine administration, the Tubazid CD_{50} increased to 184±8.2 mg/kg. The difference between the control and the experiment proved to be statistically significant. Preliminary administration of d-cycloserine did not affect the Tubazid CD_{50}; the CD_{50} in the experiment equalled 164.4±8.76 mg/kg, and the difference as compared with the control was not statistically significant.

Investigation of the LD_{50} of Tubazid gave similar results. Preliminary administration of the cycloserine racemate caused the LD_{50} to increase to 205.8±6.45, as compared to the control 175±9.6 mg/kg. Administration of the dextrorotatory cycloserine isomer did not change the LD_{50} (166.3±6.27 mg/kg).

The use of d,l-cycloserine, therefore, reduces the toxicity of Tubazid, causing a 15-18% increase in the CD_{50} and LD_{50} of this preparation, while d-cycloserine did not, in the dose used in these experiments, affect these indices.

We also found that d,l-cycloserine retards the onset of convulsions induced by the administration of Tubazid, while d-cycloserine does not have this effect. Preliminary administration of d,l-cycloserine prolonged the life span of mice given lethal doses of Tubazid by almost 150%, but no such changes were caused by the use of d-cycloserine. The data obtained in this part of the work are given in Table 2.

It was therefore established that d,l-cycloserine increases the CD_{50} and LD_{50} of Tubazid for mice and retards the development of convulsions and the time of the animals' death; none of these indices are affected by a 50 mg/kg dose of d-cycloserine. The divergence of our data as to the effects of d-cycloserine from the results obtained by Prescott et al. [10] and Monaco [8] may be due to the fact that these researchers used very large doses of d-cycloserine.

Our own data and review of the literature permit one to conclude that d,l-cycloserine is more antagonistic than d-cycloserine to the toxic effect of Tubazid.

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