POTENTIATION OF MEDICATION SLEEP BY 6-METHYLTHIOURACIL AND HYDRORUBEANIC ACID

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When the antithyroid activity of thiourea and compounds of similar structure was established [5,6,7,13-16], the use of preparations with this type of action to treat thyrotoxicosis (thiouracil, 6-methylthiouracil) became generally accepted [5,11,12,14,16].

Although these preparations have been widely used for some time, they still interest researchers [3,4,7,8,10]. This is because many problems connected with the effects of these preparations on the human and animal organisms need further study. The question of the combined effect of thyroid gland inhibitors and other pharmacological agents has received very little study.

The answer to this question is of practical as well as theoretical interest. In previous investigations [9], we showed that the preparations Antabuse and Tetrathione, which are structurally similar to certain thyroid gland inhibitors, prolong and intensify the effect of narcotic agents.

The present work examines the effect of 6-methylthiouracil and hydrorubeanic acid on the somnifacient effect of barbiturates (hexenal [hexobarbital], thiopental, medinal [barbital sodium] and Nembutal), urethan and chloral hydrate.

METHODS

The experiments were performed on 165 mice weighing 15-29 g and on 70 rats weighing 70-270 g each. Hydrorubeanic acid ($H_2N \cdot C \cdot C \cdot NH_2$, with S S), a compound very similar to thiourea which is used to determine copper in biological objects, and 6-methylthiouracil were introduced into the animals' stomachs once in a dose of 100 mg/kg, administered in the form of a suspension in 2% starch paste. In this dose, these substances caused no apparent changes in the animals. The control animals received only the starch paste. Sixty minutes after the experimental preparations and starch paste were administered, the animals were subcutaneously injected with sleep-inducing doses of the narcotics. Medinal and Nembutal were introduced into the stomach of the mice, and thiopental was administered intraperitoneally to the rats. The duration of the sleep was judged from the length of time the animals remained in the "lateral position" (from the time they took this position until the time they abandoned it). When the righting reflex of the animals was restored, the sleep was considered to have ended. The numerical data were processed by the method of variation statistics [1].

Experiments in which the difference between the averages was 2-3 or more times greater than its error were considered to have given statistically significant results [2].

RESULTS

The results of the investigations conducted are shown in the table.

We found that the experimental substances prolong and deepen the course of sleep induced by barbiturates, urethan and chloral hydrate. Hydrorubeanic acid was found to be the more efficient of the two in this respect.

The first series of experiments, performed on mice, established that the sleep of the experimental mice given a combination of hexenal and hydrorubeanic acid lasted 1682% longer than that of the control; all five experimental

mice died, while all the controls survived. Prolongation of the sleep period was also observed when hexenal was used in conjunction with 6-methylthiouracil, but this result did not prove statistically significant. 6-Methylthiouracil promoted the development of sleep in experiments with thiopental. A 30 mg/kg dose of thiopental did not induce the control mice to take the "lateral position". When 6-methylthiouracil was administered in conjunction with this dose of thiopental, however, sleep lasting an average of 248 min developed in eight out of ten mice.

Duration of Sleep Induced in White Rats and Mice by Narcotics Combined with 6-Methylthiouracil or Hydrorubeanic Acid

Preparation	Dose in mg/kg	Number of animals	Average duration of sleep (in min) X ± Sx	Difference between control and experiment and error of difference	t	Increase in sleep duration (in %)
			Mice			
Hexenal	40	20	31±6			
"	50	5	46±12			
Thiopental	30	25				
Medinal	180	15	101±15			
Nembutal	25	15	21±10			
"	35	5	28±6			
Chloral hydrate	350	5	17±6			
Urethan	1300	5	14±2			
6-Methylthiouracil + hexenal	100	10	54±16	23±17	1,3	-
	40					
Hydrorubeanic acid + [all combinations of hydrorubeanic acid given with two +s] hexanol	100	5(all died)	820±182	774±182	>3	1682
	50					
6-Methylthiouracil + thiopental	100	10(one died)	248±59	eight slept		
	30					
6-Methylthiouracil + medinal	100	10	230±24	129±28	>3	127
	180					
6-Methylthiouracil + Nembutal	100	10(one died)	266±92	245±92	2,6	1166
	25					
Hydrorubeanic acid + Nembutal	100	5	150±7	122±9	>3	435
	35					
6-Methylthiouracil + chloral hydrate	100	5(one died)	126±53	109±53	2	641
	350					
Hydrorubeanic acid + chloral hydrate	100	5(3 died)	611±175	594±175	>3	3494
	350					
6-Methylthiouracil + urethan	100	5	32±3	18±4	>3	128
	1300					
Hydrorubeanic acid + urethan	100	5(died)	378±27	364±24	>3	2600
	1300					
			Rats			
Hexenal	50	5	18±5			
Medinal	180	10	166±26			
"	160	5	105±19			
Thiopental	25	5	21±6			
Chloral hydrate	250	5	34±3			
Urethan	800	5	50±2			
6-Methylthiouracil + hexenal	100	5	52±2	34±5	>3	188
	50					
6-Methylthiouracil + medinal	100	5	280±35	114±43	2,6	68
	180					
Hydrorubeanic acid + medinal	100	5	168±6	63±20	>3	60
	160					

6-Methylthiouracil + thiopental	100 25	5	41±18	20±18	1,1	-
Hydrorubeanic acid + thiopental	100 25	5	62±14	41±15	2,7	195
6-Methylthiouracil + chloral hydrate	100 250	5	36±2	2±4	-	-
6-Methylthiouracil + urethan	100 800	5	109±13	59±24	2,4	118
Hydrorubeanic acid + urethan	100 800	5	118±15	68±15	>3	136

As the table shows, 6-methylthiouracil caused a 127% increase in the duration of sleep induced by medinal, a 1166% increase in the duration of Nembutal sleep, a 641% increase in the duration of chloral hydrate sleep and caused the sleep induced by urethan to increase 128% of the control.

After the administration of hydrorubeanic acid, Nembutal sleep lasted 435% longer than the control, while the duration of sleep induced by chloral hydrate and urethan increased respectively 3494% and 2600%. Besides the longer sleep period observed on a background of hydrorubeanic acid (experiments with chloral hydrate and urethan), the toxic effect of the narcotics was stronger, as the death of the animals in the experimental groups indicated. The toxic effect was also intensified to some extent by 6-methylthiouracil (see table).

6-Methylthiouracil did not prolong the somnifacient effect of chloral hydrate in the experiments on rats. The result observed when this substance was combined with thiopental was to some extent similar; although the duration of the sleep period did increase, the result cannot yet be considered conclusive (see table). Additional investigation is required to secure definite proof.

6-Methylthiouracil caused a 68-188% increase in the duration of the sleeps induced by hexenal, medinal and urethan.

On the background of hydrorubeanic acid, the sleep induced by medinal became an average of 60% longer than the control, thiopental sleep increased 195% and urethan sleep increased 136%. Our earlier established rule that preparations which contain the >C=S group not only possess antithyroid activity (as known), but also potentiate the effects of narcotic and hypnotic agents is corroborated by the results of these investigations. The synergism of thyroid gland inhibitors and narcotics which was observed in the experiments is evidently based on sensitization of the central nervous system to the action of hypnotic and narcotic agents, this sensitization being effected by the thyroid gland inhibitors. This hypothesis is borne out by the fact that, under the influence of the thyroid gland inhibitors, sleep developed in animals administered narcotics in subthreshold doses, i.e. doses which were not sufficient to induce sleep when used alone (experiments with thiopental).

The data obtained confirm the opinion found in the literature that thyroid gland inhibitors, unlike thyroidin [dessicated thyroid preparation], promote the development of protective inhibition in the central nervous system by weakening the stimulating and inhibitory processes [3,4,10].

On the basis of the literature data, one can assume that thyroidin and similar preparations would act to shorten the duration of medication sleep or narcosis.

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All abbreviations of periodicals in the above bibliography are letter-by-letter transliterations of the abbreviations as given in the original Russian journal. *Some or all of this periodical literature may well be available in English translation.* A complete list of the cover-to-cover English translations appears at the back of this issue.
