A COMPARISON OF THE GANGLIOBLOCKING AND CURARIFORM EFFECTS OF 3,4-DITHIAHEXANE-1,6-BIS-TRIMETHYLAMMONIUM DIIODIDE AND HEXONIUM [HEXAMETHONIUM]

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Bis-trimethylammonium derivatives in which the trimethylammonium groups are linked by a polymethylene chain have recently been thoroughly investigated in regard to their ganglioblocking and curariform effects [see 4]. Dithio analogs of these compounds of the general type:

$$(CH_3)_3\overset{+}{N} - (CH_2)n - S - S - (CH_2)n - \overset{+}{N}(CH_3)_3 \cdot 2\overset{-}{J}.$$

have not been as thoroughly studied.

Hunter [see 3] examined 5,6-dithiadecane-1,10-bis-trimethylammonium and found that it is close to decamethonium, both quantitatively and qualitatively. There are brief data [see 2] concerning the ganglioblocking activity of 3,4-dithiahexane-1,6-bis-trimethylammonium which indicate that this compound is less active than hexamethonium. 3,4-Diethiahexane-1,6-bis-trimethylammonium has not been investigated in any greater detail.

In this work, the purpose of which was to compare the pharmacological activity of hexamethonium (Hexonium) with that of its dithio anolog, we studied the comparative effect of these compounds on ganglionic and neuromuscular synapses. We made an analogous study of 4,5-dithiaoctane-1,8-bis-trimethylammonium diiodide.

Hexonium (diiodide) was obtained from S. V. Anichkov's (Active Member of the AMN SSSR) laboratory. 3,4-Dithiahexane-1,6-bis-trimethylammonium diiodide, hereinafter referred to as Dithiahexonium, and 4,5-dithiaoctane-1,8-bis-trimethylammonium diiodide were synthesized by the chemist R.G. Kostyanovskii. The dithio derivatives are colorless needles, readily soluble in water. The melting point of Dithiahexonium is 233°, that of the dithiaoctane derivative, 203-205°.

METHOD

Cats anesthetized with urethan (1 g/kg intraperitoneally) were used to study the effect of the preparations on the conduction of stimulation in the ganglia and neuromuscular synapses.

The change in the reaction of the superior cervical ganglion indicated the effect on the sympathetic ganglia. Stimulation of the preganglionic trunk of the sympathetic nerve (with electric impulses) produced a prolonged tonic contraction of the nictitating membrane, which was recorded on a kymograph tape. Solutions of the preparations were introduced into the femoral vein. Inhibition of conductivity in the ganglia induced a decrease in the tonus of the membrane or the complete relaxation of the latter. We also studied the effect of the preparations on the changes in contractions of the nictitating membrane induced by intravenous injections of cytisine (20 μ g/kg). The arterial pressure and the respiration were recorded synchronously with the contractions of the nictitating membrane.

The effect on the parasympathetic ganglia (cardiac ganglia of the vagus nerve) was measured by the changes in the depressor reaction induced by stimulation of the peripheral section of the cervical trunk of the vagus nerve.

The changes in neuromuscular conductivity were judged according to the decrease in the amplitude of the gastrocnemius muscle's contractions in response to stimulation of the peripheral section of the sciatic nerve with electric, square-wave pulses given every 5 seconds and lasting 10 microseconds each. We also studied the effect of the preparations on a frog's isolated rectus abdominis muscle.

White mice intraveneously injected with the preparations were used to study the toxicity of the latter.

RESULTS

Effect on the sympathetic ganglia. After the administration of Dithiahexonium in a dose of 0.1 mg/kg, the nictitating membrane relaxed slightly; in this dose, the preparation had an effect lasting 5-7 minutes. The effect of the dithiaoctane analog in the same dose was similar in intensity and duration, but Hexonium produced the same effect when used in a dose of 0.03 mg/kg (Fig. 1).

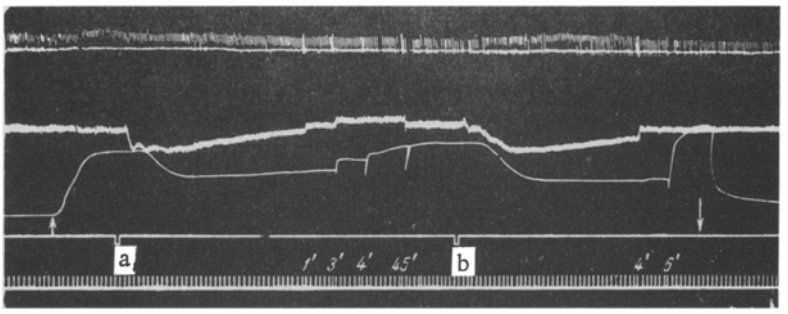

Fig. 1. Effect of Dithiahexonium and Hexonium on conduction of nervous excitation in the superior cervical ganglion. Experiment on cat weighing 3.4 kg. Urethan anesthesia. Curves show (from top to bottom): Respiration, arterial pressure; tonus of nictitating membrane; Dithiahexonium injection (a) – "OF 1465", 0.1 mg/kg and Hexonium injection (b) – 0.03 mg/kg; indications of time in 5-second marks and stopping of kymograph. The arrows (↑ ↓) mark the beginning and end of stimulation of the sympathetic nerve.

Dithiahexonium had a stronger effect lasting 10-12 minutes when its dose was increased to 0.2 and 0.3 mg/kg. Effects of similar force and duration were produced by Hexonium in doses of 0.075 and 0.1 mg/kg respectively.

Therefore, although Dithiahexonium has a pronounced ganglioblocking effect, it is approximately 1/3 as active as Hexonium. The effect of the dithiaoctane analog is the same as that of Dithiahexonium.

In a dose of 0.2 mg/kg, Dithiahexonium and the dithiaoctane derivative lessened the contraction of the nictitating membrane, the pressor reaction and the respiratory stimulation induced by the intravenous injection of cytisine. In this dose, the two preparations were only effective during the first few minutes after their administration; cytisine's effect was fully restored after 10-12 minutes.

Hexonium had an effect similar in intensity and duration when used in a dose of 0.05 mg/kg. When the dose of Hexonium was raised to 0.2 mg/kg, the preparation caused a prolonged (lasting more than an hour) reduction of the reactions of the arterial pressure, respiration and nictitating membrane to the injection of cytisine.

Effect on the parasympathetic ganglia. In a dose of 0.1 mg/kg, Dithiahexonium induced a 15-20% decrease in the depressor reaction of the arterial pressure in response to electric stimulation of the vagus nerve. The reaction was restored after 5-6 minutes. Hexonium had an analogous effect in a dose of 0.03 mg/kg.

In a dose of 0.3 mg/kg, Dithiahexonium caused a 30-33% decrease in the depressor reaction; the original reaction was restored 10-12 minutes after the injection of the preparation. The dithiaoctane analog had the same effect.

In a dose of 0.1 mg/kg Hexonium caused the depressor reaction to decrease more than 50%, and 50-60 minutes later, the original value of the reaction had not yet been restored.

Therefore, the effect of Dithiahexonium and its dithiaoctane analog on the parasympathetic ganglia is less than 1/3 as strong as that of Hexonium.

Effect on neuromuscular conductivity. In doses of 0.4-0.8 mg/kg, Dithiahexonium decreased the amplitude of muscle contractions and, in some experiments, effected a complete block of neuromuscular conductivity (Fig. 2,a). The effect of the preparation in these doses lasted 12-20 minutes. In doses of 1 mg/kg or more, Dithiahexonium not only blocked neuromuscular conductivity, but usually caused a 5-8 minute respiratory arrest.

Hexonium had considerably less effect on neuromuscular conductivity. Only after the injection of Hexonium in a dose of 20 mg/kg did we observe a brief (lasting 15-20 seconds) decrease in the amplitude of the muscle contractions. A greater decrease in the amplitude of the contractions was observed after the injection of Hexonium in a dose of 40 mg/kg (Fig. 2,b).

Therefore, the effect of Dithiahexonium on neuromuscular conductivity is more than 100 times stronger than that of Hexonium. The dithiaoctane analog was found to be even more active. In a dose of 0.1-0.2 mg/kg, it produced the same effect as Dithiahexonium in a dose of 0.4-0.8 mg/kg (Fig. 2,c).

Because of the strong inhibitory effect of Dithiahexonium on neuromuscular conductivity, it was interesting to determine the character of the curariform effect exerted by this compound. Curariform preparations of the bis-trimethylammonium series (decamethonium) are known

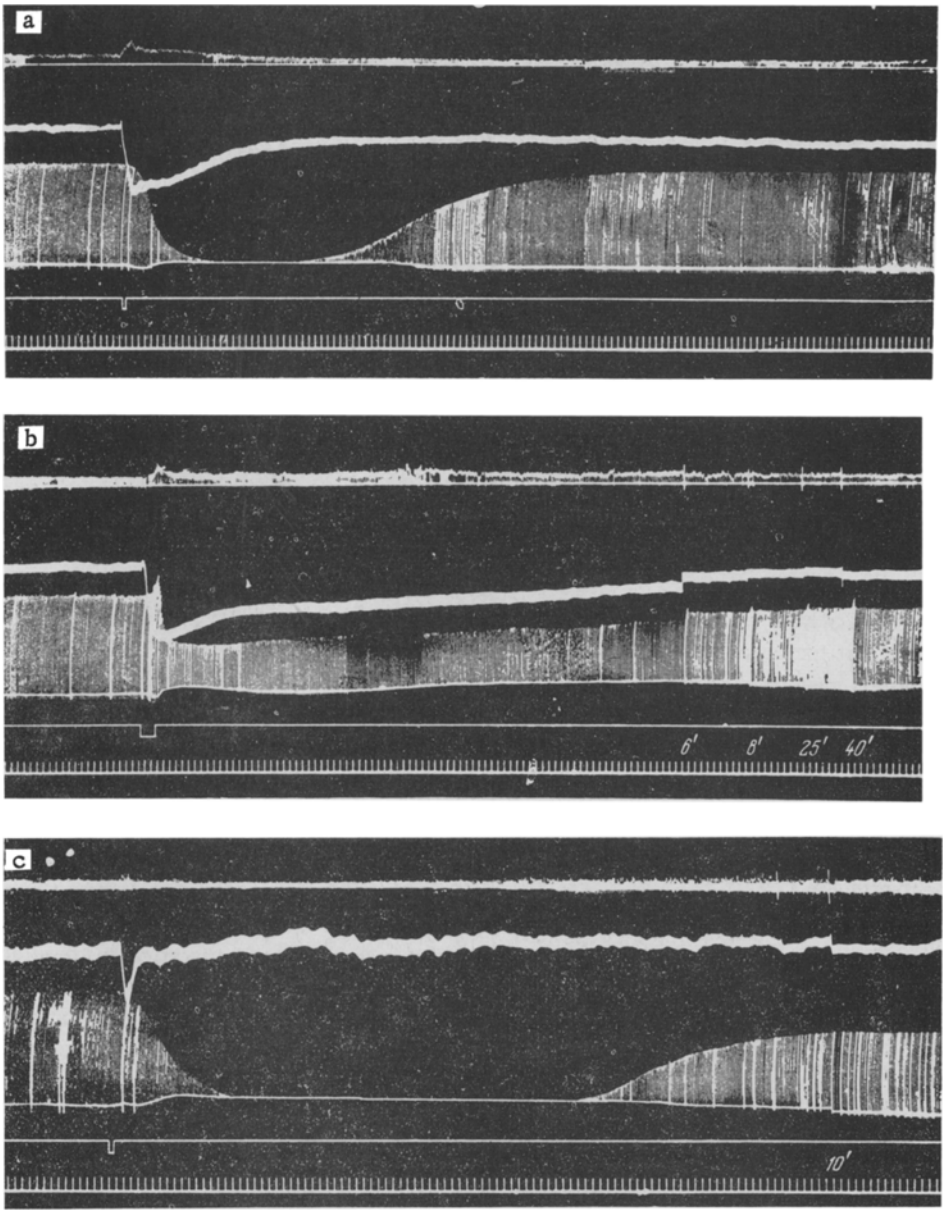

Fig. 2. Effect of the experimental preparations on neuromuscular conductivity. Experiments on a cat weighing 2.6 kg. Urethan anesthesia. Curves (from top to bottom) show: respiration, arterial pressure, contraction of gastrocnemius muscle, administration of substances, time in 15-second marks. a) Effect of Dithiahexonium ("OF 1465" - 0.4 mg/kg); b) - effect of Hexonium (40 mg/kg); c) effect of dithiaoctane analog ("OF 1521" - 0.12 mg/kg).

to belong to the group of substances having the depolarizing type of action. In experiments performed on cats, we found that the blocking effects of Dithiahexonium and the dithiaoctane analog are intensified by the intravenous injection of Proserine [neostigmine] (0.15 mg/kg). The administration of Diplacin [curare simulant] under the same experimental conditions (dose = 0.2-0.8 mg/kg) weakened the blocking effects of Dithiahexonium and the dithiaoctane analog.

Therefore, the effect of these two dithia derivatives is like that of the depolarizing substances.

It should be mentioned that the dithiaoctane derivative, when used in a concentration of at least $1 \cdot 10^{-5}$, caused a frog's rectus abdominis muscle to contract. Dithiahexonium (in concentrations of $1 \cdot 10^{-6}$ to $2 \cdot 10^{-3}$) caused no apparent contraction of the muscle.

Toxicity for white mice. Experiments were performed on mice weighing 16-17 g. Each dose was tested on 5 animals, which were observed for a period of three days from the time the preparations were administered.

The first signs of intoxication appeared after the injection of Dithiahexonium in a dose of 7.5 mg/kg. We observed inhibition, mild tremor and unsteady gait in the mice; with larger doses (10-12.5 mg/kg), brief respiratory arrest occurred. The LD_{50}, calculated according to Kerber's method, equalled 14.8 mg/kg. The LD_{50} of the dithiaoctane derivative was 4.7 mg/kg.

Hexonium caused inhibition, tremor and, in large doses (60-70 mg/kg), unsteady gait in the mice. The absolute lethal dose was 80 mg/kg. The animals died with symptoms of respiratory arrest 2-7 minutes after the injection. The LD_{50}, calculated according to Kerber's method, equalled 62.8 mg/kg.

Therefore, Dithiahexonium was found to be more than 4 times more toxic to white mice than Hexonium, while the dithiaoctane analog was more than 13 times more toxic than the latter.

The investigations conducted show that the substitution of the two CH_2 groups in the polymethylene chain of Hexonium by two sulfur atoms substantially alters the pharmacological activity of the compound, changing both the ganglioblocking and the curariform activity of the preparation.

The ganglionic properties are decreased. Our experiments with the tonicized membrane and the injection of cytisine showed that Dithiahexonium's effect on the sympathetic ganglia is at least 1/3 as strong as that of Hexonium; the experiments studying the effect on the parasympathetic ganglia of the cardiac branches of the vagus nerve gave approximately analogous results.

Curariform activity, on the other hand, increases considerably. Our experiments showed that the effect of Dithiahexonium on neuromuscular conductivity is more than 100 times stronger than that of Hexonium.

According to the data of Paton and Zaimis [4] and of Barlow and Ing [1], the most active ganglioblocking substances of the bis-trimethylammonium derivatives are compounds with five or six methyl groups, in which the distance between the quaternary nitrogen atoms is about 7.7 A. Compounds in which the distance between the nitrogen atoms is about 14-15 A possess a pronounced curariform activity. In Dithiahexonium, this distance is 8.76 A. Therefore, the distance between the quaternary nitrogen atoms is essentially the same in both Dithiahexonium and Hexonium. These two compounds differ substantially in pharmacological activity: Dithiahexonium's ganglioblocking activity is weaker than that of Hexonium, but its effect on the neuromuscular synapses is considerably stronger than that of the latter.

Moreover, Dithiahexonium is considerably more toxic than Hexonium.

Although the dithiaoctane derivative has about the same effect as Dithiahexonium on ganglia, its curariform activity and toxicity are considerably greater.

SUMMARY

The authors studied the effect of the following preparations on the sympathetic and parasympathetic ganglia and on neuromuscular transmission: Hexonium, 3,4-dithiahexane-1,6-bis-trimethylammonium diiodide (Dithiahexonium) and 4,5-dithiaoctane-1,8-dis-trimethylammonium diiodide.

The effect of Hexonium on the ganglii is about triple that of Dithiahexonium. The latter is more active than Hexonium in its effect on neuromuscular transmission (approximately 100 times). Dithiahexonium is 4 times more toxic than Hexonium.

The dithiaoctane derivative does not significantly differ from Dithiahexonium as to effect on ganglia, but possesses a higher curare-like effect and toxicity.

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