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NEUROMUSCULAR BLOCKADE BY STREPTOMYCIN AND DIHYDROSTREPTOMYCIN

BY

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Both streptomycin and dihydrostreptomycin in large doses produced neuromuscular blockade in different types of skeletal nerve-muscle preparations. Streptomycin had a quicker, more marked and a longer-lasting action than dihydrostreptomycin. Neostigmine reversed a partial block of streptomycin, but a complete neuromuscular block remained unaffected. Calcium ions antagonized the neuromuscular block of streptomycin rapidly but incompletely.

Both streptomycin and dihydrostreptomycin may cause a number of untoward phenomena, particularly injury to the nervous system and hypersensitivity reactions. The main toxic side-effect in the chronic use of streptomycin is damage to the vestibular mechanisms and the eighth cranial nerve, which was first described in man by Hinshaw and Feldman (1945) and in experimental animals by Molitor and his collaborators (1946, 1950). The latter authors also showed that streptomycin in high dosage caused death in experimental animals as a result of respiratory failure. Brazil and Corrado (1957) studied the motor effects of streptomycin in dogs and in pigeons, and they found that streptomycin possesses neuromuscular blocking properties which are similar to those produced by magnesium. Calcium and neostigmine suppressed the motor effects of acute streptomycin intoxication. Brazil and Corrado (1957) employed a very high dose (110 mg./kg.) to demonstrate the neuromuscular blocking effect of streptomycin in dogs, and the effect was not compared with that of dihydrostreptomycin, which is known to differ from streptomycin in toxicity in certain respects. Recently Loder and Walker (1959) have reported 3 cases of muscular paralysis in patients who were kept on streptomycin treatment for a period varying from 3 days to 3 months with usual dosage. It was therefore thought necessary to investigate the pharmacological actions of streptomycin on various types of skeletal muscles and compare its effects with those of dihydrostreptomycin. The results of such a study are reported in this paper.

METHODS

Streptomycin and dihydrostreptomycin were purchased locally of " Hindustan Antibiotics " make; the purity was stated by the manufacturers to conform to the standards prescribed by the *British Pharmacopoeia.*

Rat Phrenic Nerve-Diaphragm Preparation.—This was prepared as described by Bülbring (1946). Ten adult rats were used. The isolated tissues were suspended in a 60 ml. bath, containing Tyrode solution with double the amount of dextrose. Single shocks at rates not exceeding 8/min. were applied to the nerve from a square wave stimulator, at 10 to 12 volts and 0.5 to 1.0 msec. duration. Drugs were added directly to the bath through a very fine polythene tube attached to a hypodermic needle.

Dog Sciatic-Gastrocnemius Preparation.—Experiments were performed in 10 dogs anaesthetized with sodium pentobarbitone (35 mg./kg.) injected intraperitoneally. One leg was immobilized and the sciatic nerve was exposed between the hamstring muscles and sectioned. The peripheral stump of this nerve was placed on a non-polarizing bipolar electrode. The contractions of the gastrocnemius muscle were recorded with an isometric lever. The muscle was stimulated through the sciatic nerve by a square wave stimulator at a rate of 8/min. at 10 to 12 volts and 0.5 to 1.0 msec. duration. Retrograde injections of drugs were made through the cannulated common iliac artery.

Frog Rectus Abdominis Muscle Preparation.—Frogs were pithed and the rectus abdominis muscle was dissected and suspended in a 10 ml. bath containing oxygenated frog-Ringer solution at room temperature. The contractions produced by acetylcholine chloride (0.10 to 1.0 μg./ml.), when added to the bath and left in contact with the tissue for 90 sec., were recorded. Streptomycin and dihydrostreptomycin were added to the bath 30 sec. before a subsequent addition of acetylcholine and the contractions again recorded for 90 sec. The bath was then washed out. Between successive additions of acetylcholine there was at least an interval of 8 min., or until the muscle recovered from the effect of the streptomycins.

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RESULTS

Effect on Rat Diaphragm Preparations. — Streptomycin and dihydrostreptomycin were tested in concentrations ranging from 10 μg. to 1.5 mg./ml. Neither substance affected the contractions in concentrations up to 200 μg./ml. However, at 0.25 mg./ml. streptomycin sulphate produced a mean reduction of 44%, and dihydrostreptomycin at the same dose produced a mean reduction of 19%. Higher concentrations produced proportionately greater effects, a maximum of 94% reduction with streptomycin 1.5 mg./ml., and of 71% with the same dose of dihydrostreptomycin (Table I). It was observed that there was a short latent period in the onset of action with dihydrostreptomycin which was not seen with streptomycin. Recovery of the diaphragmatic contractions was complete after washing out the drug, the recovery time varying according to the dose. Higher concentrations took a longer time for the complete recovery of the muscle. Muscle treated with dihydrostreptomycin took a shorter time for recovery in comparison with streptomycin. The response to direct excitation of the rat diaphragm did not alter in any of the experiments.

TABLE I

THE MEAN REDUCTION IN MUSCULAR CONTRACTIONS PRODUCED BY STREPTOMYCIN AND DIHYDROSTREPTOMYCIN IN THREE DIFFERENT PREPARATIONS

Muscle Preparation	Dose	% Reduction in Contraction	
		Streptomycin	Dihydrostreptomycin
	mg./ml.		
Rat phrenic nerve-diaphragm	0·25	44	19
	0·5	57	52
	1·0	94	71
	mg./kg.		
Dog gastrocnemius-sciatic nerve	10	20	13
	20	83	16
	40	100	24
	mg./ml.		
Frog rectus abdominis	5	37	11
	10	40	27
	20	46	38

Effect on Dog Gastrocnemius Sciatic Preparation. — Streptomycin and dihydrostreptomycin were injected intravenously in doses ranging from 1 mg. to 40 mg./kg. body weight. Doses below 8 mg./kg. did not affect the contractions of the gastrocnemius, whereas higher doses produced graded reductions in the amplitude of the contractions (Table I and Fig. 1*a*). The effect of dihydrostreptomycin was not only slower to develop but the overall depression in muscular contraction was much less (Table I and Fig. 1*b*). As in the rat diaphragm, recovery was quicker with dihydrostreptomycin.

Neostigmine given intravenously in 1.5 mg. doses antagonized the effect of a partial neuromuscular block of streptomycin (Fig. 2*a*), but in the presence of total neuromuscular block neostigmine failed to restore the contractions (Fig. 2*b*). Calcium chloride, 0.5 mg./kg., on the other hand, antagonized the neuromuscular block of streptomycin quickly, but not completely (Fig. 2*b*).

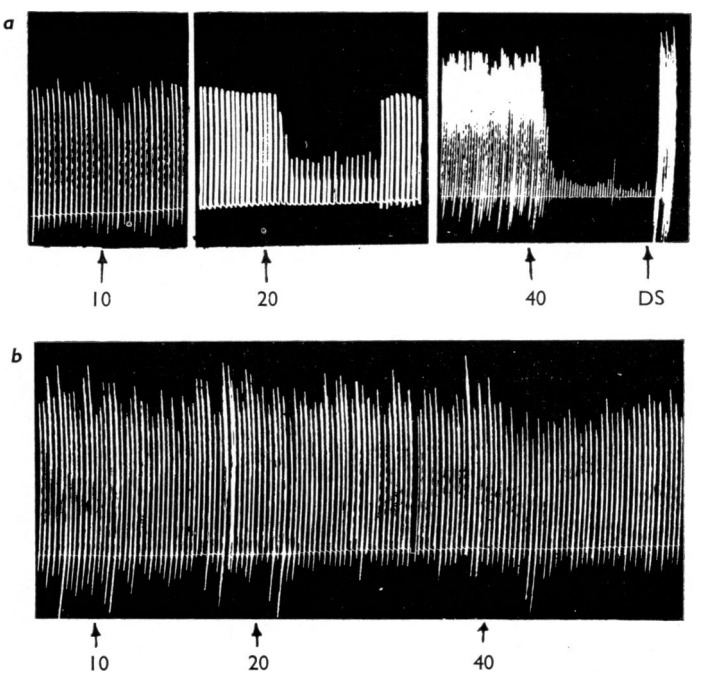

FIG. 1.—Dog gastrocnemius-sciatic nerve preparation. Contractions induced by indirect stimulation of the sciatic nerve or by direct stimulation of the muscle. In (*a*) effect of streptomycin 10, 20, and 40 mg./kg. and of direct stimulation (DS). In (*b*) effect of dihydrostreptomycin 10, 20, and 40 mg./kg.

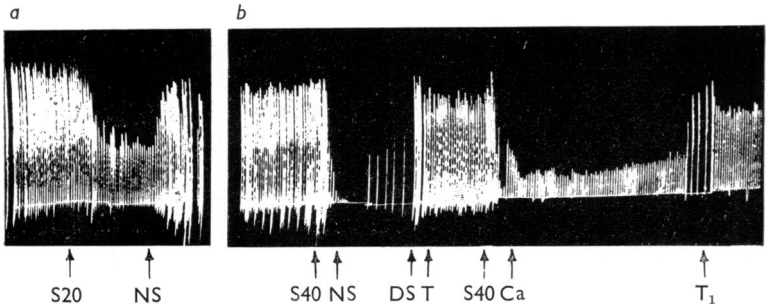

FIG. 2.—Dog gastrocnemius-sciatic nerve preparation. Contractions induced by indirect stimulation of the sciatic nerve or by direct stimulation of the muscle. Effect of streptomycin and antagonists. At S20, 20 mg./kg. streptomycin. NS, neostigmine 0.15 mg./kg. S40, 40 mg./kg. streptomycin. DS, direct stimulation. T, time of recovery—30 min. after first injection of streptomycin. T_1, time of recovery—25 min. after second injection of streptomycin. Ca, calcium chloride 10%—0.5 ml./kg.

Effect on Frog Rectus-Abdominis Muscle Preparation.—The effects of streptomycin and dihydrostreptomycin were tested on the acetylcholine-induced contractions of the rectus abdominis muscle. Graded doses of streptomycin and dihydrostreptomycin were given ranging from 1 mg. to 20 mg./ml. Doses from 5 to 20 mg./ml. inhibited the contractions of the rectus muscle to a varying degree, and the effect was proportional to the concentration of drug in the bath. Streptomycin had a greater effect than dihydrostreptomycin; 20 mg./ml. of streptomycin depressed the muscle so as to prevent its recovery for as long as 2 hr. even after repeated washings of the muscle. In contrast to this, recovery of the muscle was complete in the case of dihydrostreptomycin after a period of 1 hr. (Fig. 3*a* and *b*).

DISCUSSION

It has been clearly demonstrated that streptomycin can cause muscular paralysis in high doses, thus confirming the observations of Brazil and Corrado (1957). The muscular paralysis is much more marked with streptomycin than dihydrostreptomycin when equal doses are used. The onset of action is more rapid with streptomycin and the recovery time of muscle is definitely shorter with dihydrostreptomycin. The muscular paralysis seems to be due to neuromuscular blockade produced by streptomycin, since the direct excitability of the different muscle preparations was never found to be decreased in any of the experiments. Neuromuscular blockade was demonstrated in three different types of skeletal muscle preparations, which included mammalian as well as amphibian skeletal muscles. This lends support to the view that all types of muscles are susceptible to the neuromuscular blocking action of streptomycin in high doses. In contrast to Brazil and Corrado (1957), who studied only one type of skeletal muscle preparation (the sciatic-tibialis anticus of the dog) and used a high dose (110 mg./kg.), in these experiments we found that a dose of 40 mg./kg. produced complete paralysis and smaller doses had proportionately a smaller effect. It is therefore not unlikely that streptomycin in ordinary therapeutic doses may be capable of producing neuromuscular blockade in certain isolated cases, as has been observed by Loder and Walker (1959). The neuromuscular blockade with streptomycin can possibly occur as

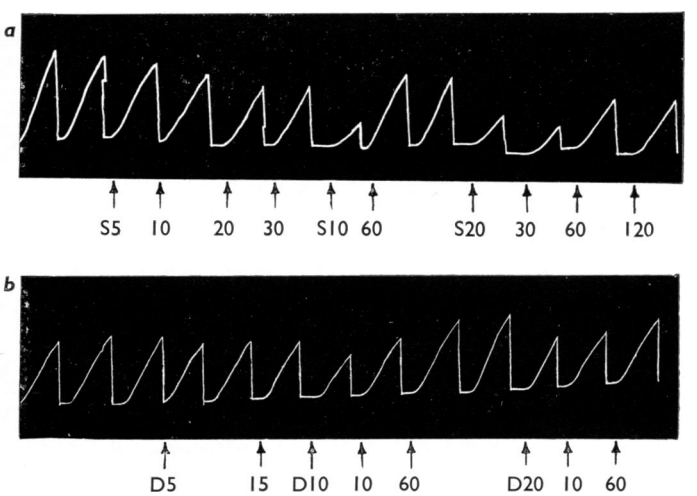

FIG. 3.—Frog rectus abdominis suspended in a 10 ml. bath containing oxygenated frog-Ringer solution at room temperature. Contractions to acetylcholine (1.0 μg./ml.). In (*a*) effects of streptomycin and in (*b*) effects of dihydrostreptomycin. Numbers indicate time intervals in min. Acetylcholine was left in the bath for 90 sec. and then washed out. At S5, 5; S10, 10; and S20, 20 mg./ml. streptomycin. At D5, 5; D10, 10; and D20, 20 mg./ml. dihydrostreptomycin.

a result of cumulative action of the drug which is usually administered over a prolonged period.

Neostigmine antagonizes the effect of streptomycin only when there is a partial neuromuscular block. In the presence of complete neuromuscular block the effect of neostigmine is negligible. Calcium ions can antagonize quickly but less completely the effect of streptomycin on skeletal muscles. Similar results have been reported by Corrado, Ramos, and De Escobar (1959) for the neuromuscular blocking action of neomycin. It is thus likely that the neuromuscular blocking actions of neomycin and streptomycin involve a common mechanism of action.

Another interesting feature of the present investigation is the difference in action of streptomycin and dihydrostreptomycin. Clinically streptomycin differs from dihydrostreptomycin regarding the injury it is likely to cause to the nervous system in general and damage to the eighth cranial nerve in particular. We have found that neuromuscular blockade produced by dihydrostreptomycin is not only slow to develop, but the depression of muscular contraction is less and the time for recovery of the muscles is quicker, as compared with streptomycin.

The present experiments have thus not only confirmed the clinical case reports of Loder and Walker (1959), but also suggest that the danger of neuromuscular blocking action of streptomycin would be greatly diminished by using dihydrostreptomycin. On the other hand, dihydrostreptomycin may cause a greater incidence of auditory damage than streptomycin (Crofton, 1960). The antagonists to the toxicity on skeletal muscles resulting from the use of streptomycin, as suggested from these observations, should be both neostigmine and calcium. Simultaneous administration of calcium throughout streptomycin therapy is suggested as a prophylactic measure against the toxicity of streptomycin on skeletal muscles.

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