THE CONVULSIVE EFFECTS OF STREPTOMYCIN TOPICALLY APPLIED TO THE CEREBRAL CORTEX*

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(Received for publication March 10, 1947)

This investigation of the possible toxic effects of streptomycin on the central nervous system was prompted by recent observations of the untoward reactions of penicillin.6,11 The convulsive threshold of streptomycin has been determined in rabbits, dogs and monkeys (Macacus rhesus). This information should serve as a guide in the future clinical use of streptomycin. The results confirm and amplify the report of Walker and his coworkers.10

METHODS

The effects of the cortical application of streptomycin were determined after prior preparation of adequate approaches during surgical anesthesia. Various arrangements of openings were made over the premotor, motor and occipital cortices of 33 rabbits, 8 dogs and 4 monkeys.

In rabbits analgesia of the scalp was accomplished by infiltration of the operative area with 1 per cent procaine solution. Burr holes then were made over the motor cortex on each side of the skull approximately 1 cm. from the midsagittal line.

Sodium ethyl (1-methyl butyl) thiobarbiturate (pentothal sodium) was used for anesthesia of dogs, and openings in the skull were made bilaterally over all three of the designated cortical regions at an estimated distance of 1.5 cm. from the midline. Brass screws of lengths approximating the thickness of the skull were inserted in the burr holes of some of the animals which were to be used in repeated tests. Each screw had a central hole just large enough to permit passage of a No. 26 gauge hypodermic needle.

Diethyl ether, administered by open technique, was used as the anesthetic agent for the monkeys. Burr holes were made over the corresponding cortical regions and at approximately the same distance of 1.5 cm. from the midline as in the dog.

Acute experiments with all three species were performed by inserting a bent, blunt 26 gauge needle under the dura mater by direct vision and then applying a solution of streptomycin upon the cortex of the selected exposed region. The burr hole then was plugged with bownax. In chronic experiments the application was made with a blunted 26 gauge needle of a length previously determined just to reach through the central hole of the brass screw and to permit administration of the drug upon rather than into the cortex. To reduce the possibility of an increase in intracranial pressure the total volume of fluid injected usually was less than and never exceeded 0.5 cc. and applications were made over a 30-second interval. Following any injection the animals were watched continually for at least 2 hours and then for the next 24 to 48 hours periodic observations were made.

Convulsions were determined by such direct inspection, and on 3 of the monkeys EEG recordings were made to determine alterations in cortical activity. For the latter tests an intravenous administration of a curare solution was made, after which an endotracheal tube or rubber catheter was placed in the trachea and through it artificial respiration was maintained to provide adequate oxygenation throughout the test.

* Aided in part by a grant from the Wisconsin Alumni Research Foundation.
The effects of different types of streptomycin were tested by using either the sulfate or the hydrochloride salt. Dilution was made with normal saline solution or sterile distilled water. Primarily the dilution was such that 5 mg. of active streptomycin was contained in 0.1 cc. of solution. As the study progressed and higher concentrations of the drug were desired, the dilution was made such that 20 mg. were contained in 0.1 cc. of solution. With such a concentration of the drug the total volume of fluid administered was kept at or below 0.5 cc.

To compare the relationship of any convulsive effects of streptomycin to its bactericidal properties, various attempts were made to inactivate the solutions of the drug. Inactivation proved to be surprisingly difficult. The methods employed were: (1) autoclaving solutions at 250°F. and 15 pounds pressure for one hour on 5 successive days. This procedure turned the pale yellow solution to an intense dark brown color. One sample still contained a potency of 60 mg./cc.; a reduction from the original 200 mg./cc. The antibiotic potency of all the streptomycin solutions was determined by the serial dilution method with a strain of Bacillus subtilis having a sensitivity of 0.3 μ/cc. (2) Semi-carbazide hydrochloride in concentrations of 60 mg./cc. added to streptomycin solution containing 200 mg./cc. completely inactivated the antibiotic after being in contact with it for several days. (3) Cysteine hydrochloride, 400 mg./cc., completely inactivated streptomycin solution containing 200 mg./cc. Cysteine hydrochloride in a concentration of 3 mg./cc. did not inactivate it.

**RESULTS**

In rabbits, 10 to 15 minutes after an injection there was a decrease in general bodily activity. This was followed by adverse head movements to the side opposite that of the cortical application of the streptomycin. There then ensued focal seizures of myoclonic jerking of the contralateral extremities lasting for several hours. Finally, there was a period of post-convulsive weakness of 12 to 24 hours' duration. This type of response to streptomycin was classified as a minor seizure.

Major seizures were those in which the phase of adverse head movements was followed by extreme hyperirritability simulating strychnine convulsions. Generalized tonic-clonic seizures of status epilepticus duration occurred. There was extreme vocalization and cart-wheel bodily gyrations succeeded by intervals of exhaustion. The marked seizure pattern frequently returned spontaneously or was resumed by the stimulation of merely touching the animal. In 4 of 6 rabbits death from extreme post-convulsive depression and exhaustion ensued within 4 hours. Such results are summarized in Table 1. It can be noted also that in the different groups of animals given dosages of streptomycin, increasing by 5 mg. increments, the severity of reactions also increased. Thus in 6 animals given a 15-mg. application, but two had minor seizures, while of 10 animals given 30 mg. all had convulsions, 6 of which were of the major type.

In dogs the cortical application of streptomycin was followed within 15 to 20 minutes by a decrease in generalized bodily activity and the animal had detectable central depression. Thirty minutes after application of the drug adverse movements of the head to the contralateral side were noted and after a further 15 minutes myoclonic jerking of the contralateral extremities ensued. Such reactions were considered as minor seizures. Major reactions were attained when the activity proceeded to generalized convulsive movements with extension of the neck, salivation, and stupor which