EXPERIMENTAL OBSERVATIONS ON THE PREVENTION OF SEIZURES BY INTRAVENOUS PROCAINE INJECTIONS*

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Although great strides have been made in the treatment of epilepsy, a continuous and vigorous search is being made widely for new agents that may supply some additional measure of control to aid patients suffering from this severely incapacitating disorder. For this reason, it was felt appropriate to report experimental observations made recently concerning transient, but very effective anticonvulsive properties of procaine hydrochloride.

During the course of a series of experiments on cortically induced seizure discharge in monkeys, it was found that convulsions could not be elicited even from most highly epileptogenic zones if the animal had been given an intravenous injection of procaine preceding the application of the initiating stimulus. This protection persisted for upwards of 30 minutes and apparently did not depend upon the induction of a somnolent state in the animal. These observations were extended by testing the capacity of procaine and related agents to protect monkeys against seizures induced by a technique identical with that employed clinically in electroshock therapy.

During the course of these studies, it came to our attention that the phenomenon under investigation has been noted and extensively explored recently by Bernhard and Bohm in Sweden and that attention is being given it elsewhere. The observations reported here confirm in general the protective effects of procaine hydrochloride against experimentally induced seizures.

EXPERIMENTAL PROCEDURE

Initial observations were made upon 2 monkeys (Macacus mulatus) in which the seizure was elicited by a stimulus (5–15 V., 50 c./sec., 1 msec. for 3 sec.) applied directly to the premotor cortex. The craniectomy exposure had been made under ether anesthesia, the areas of pressure and incision being injected with Novocain. The anesthesia was terminated and the animal was immobilized by curare (d-tubocurarine), respirations being maintained artificially. Recordings of seizure activity

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were made on a Grass Model III EEG amplifier and ink-writer (8 channels) from bipolar concentric nicrome wire electrodes inserted stereotaxically into deep structures and from silver ball electrodes applied directly to the cortex. For control, a diffuse seizure was elicited by cortical stimulation. Subsequently, 10 ml. of procaine hydrochloride were injected intravenously in 1 min., throughout which time electroencephalographic tracing was made. The stimulus was then reapplied immediately and at 10-min. intervals after the completion of the injection, the effect upon the electroencephalographic tracing being recorded.

Subsequent observations were made upon 10 normally wakeful monkeys secured to an animal board by a specially devised head holder and by restraints of extremities. Bipolar electroencephalographic recordings were made between needle electrodes, one applied to each frontal and each parietal region in the calvaria. The seizure-inducing stimulus was applied bitemporally from an Offner Electric Shock Therapy Apparatus, Type 732. Initial assessments were made upon 3 animals to determine the optimum parameters of stimulus for inducing reproducible seizures. In these experiments, 200 to 600 mA. of 0.1 to 0.4 sec.' duration were evaluated, but for the study itself, a current of 200 mA. for 0.2 sec. was consistently employed.

In each experiment, an initial shock was applied so that the nature and duration of the recorded and observed seizure could be noted for control. When the record had returned to a pre-stimulus state and the animal appeared normal again, the drug to be tested was injected intravenously (usually within a period of 2 min.) during continuous electroencephalographic recording. The response of the animal to the shock was then tested in 5 min. and at 5- to 10-min. intervals thereafter until the induced seizure again approximated that resulting from the control stimulus.

In the course of the study, the effects of procaine hydrochloride, procaine amide, Xylocaine,* para-aminobenzoic acid and dimethyl-aminoethanol were evaluated. In some instances two drugs were tested successively and even repeatedly during the same experiment in order to compare, particularly, the protective effect of procaine after a different substance had proved ineffective in blocking a seizure. Additionally, some animals were used for repeated experiments after it was observed that the injections or shocks had no prolonged or deleterious effects upon them. In all, 27 injections were evaluated in 10 animals.

RESULTS

Initially, it was necessary to determine optimum parameters of a stimulus that would induce constantly reproducible seizures in each animal at regular (preferably short) intervals. It was found that the nature and duration of a seizure excited in different animals varied somewhat but, with threshold excitation, the convulsive episode for each individual subject remained quite constant. Increasing the strength of current above 200 mA. and the duration of the stimulus above 0.2 sec. prolonged the tonic phase of the discharge somewhat but did not otherwise alter its appearance. Moreover, the reproducibility of seizures was not significantly affected by the interval at which shocks were applied so long as this interval remained above 5 min. Thus, a characteristic convulsive attack for each subject could

* Xylocaine, Astra. (dimethyl aminoaacetate, lidocaine).