The toxicity of the drug is a deterrent to its use in the mass treatment of *S. haematobium* in the Sudan.

I am indebted to Brigadier J. S. K. Boyd for the supplies of nilodin used in the cases here recorded; to Dr. R. Kirk for his help and encouragement; and to the Director, Medical Services, Ministry of Health, Sudan, for permission to publish these observations.

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SELF-EXPERIMENTS WITH SUCCINYL- CHOLINE CHLORIDE

A NEW ULTRA-SHORT-ACTING MUSCLE RELAXANT

BY

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The purpose of this paper is to describe the action, in man, of a new synthetic muscle relaxant. Our tests were carried out with the aim of proving the safety and specific action of succinylcholine chloride (S.C.C.) as a short-acting curarizing agent for patients under anaesthesia.

With the muscle relaxants in use in clinical anaesthesia a more superficial plane of general anaesthesia can be maintained, to the benefit of the patient. The introduction of curare (Griffith and Johnson, 1942) was followed by the development of synthetic relaxing agents, the best known of which to-day are "flaxedil" (gallamine triethyl iodide) (Bovet, Depierre, *et al.*, 1947, 1949; Mushin *et al.*, 1949) and decamethonium iodide or bromide ("eulissin," "syncurine," C10) (Paton and Zaimis, 1948, 1949; Organe, 1949; Vetten and Nicholson, 1950). The lack of sufficient controllability, the occasional prolonged curarization, and the more or less marked side-effects (release of histamine and blockade of the autonomic ganglia) are the main disadvantages of all the compounds mentioned, be their paralyzing effect due to a true blockade at the neuromuscular junction, as with D-tubocurarine and flaxedil, or due to depolarization of the end-plate and its surrounding, as is the case with decamethonium (Alam *et al.*, 1939; Comroe and Dripps, 1946; Vetten and Nicholson, 1950; Burns and Paton, 1951).

Succinylcholine iodide (S.C.I.) was first described by Bovet, Bovet-Nitti, *et al.* (1949). Its strong paralyzing power was recognized in animals, but no clinical tests were undertaken. Ginzel, Klupp, and Werner (1951a, 1951b, 1951c), at the Pharmacological Institute of Vienna University, examined thoroughly both S.C.I. and S.C.C.

The Properties of S.C.C.*

The chemical formula of S.C.C. is

*The makers, Oesterreichische Stickstoffwerke A.G., Linz, Austria, kindly furnished the necessary amounts of S.C.C. for these experiments and the clinical evaluation. The drug was named "M115" when in the experimental stage, and has now been registered under the name of "Iysthenon."

Physical Properties.—S.C.C. is supplied (as dihydrate) in 5-ml. ampoules containing 20 mg. of the substance in 1 ml. The solution is stable and has frequently been kept for several weeks outside the refrigerator without any decomposition becoming apparent. It is miscible with solutions of thiopentone and also with pethidine. No decrease of the usual effect could be observed when the drug was used in any of these mixtures.

Pharmacology.—S.C.C. was tested in frogs, cats, pigeons, and dogs in comparison with other compounds with a similar chemical structure (Ginzel *et al.*, 1951a, 1951b, 1951c). The entire series showed nicotine-like stimulating effects as well as muscular paralysis. S.C.C. had the strongest neuromuscular blocking effect and the weakest stimulating action to the autonomic ganglia. In artificially ventilated cats some slight rise in blood pressure did not occur until doses as high as several hundred times the paralyzing dose were being given. The paralyzing effect on the skeletal muscle is due to the same mechanism as with decamethonium: depolarization of the end-plate region (Ginzel *et al.*, 1952). Its action, therefore, is not counteracted by anti-choline-esterases as is the case with D-tubocurarine and flaxedil. It may even be prolonged and intensified to some extent. There appears to be the same antagonism between S.C.C. and curare as has previously been described for decamethonium and curare (Paton and Zaimis, 1949). Since S.C.C. is probably broken up by enzymatic hydrolysis into the non-effective monocholine ester of succinic acid and free choline within a matter of minutes, no antidote is felt to be needed in clinical practice.

Methods and Dosage

From previous tests with other synthetic curarizing agents (Mayrhofer and Hassfurth, 1951) the fact was known that sensibility to these compounds varies widely between different animals and humans.

For the self-experiments on an unanaesthetized 30-year-old male (O. K. M.) of 176 lb. (80 kg.) body weight only the intravenous route was used. In the first three experiments the injections were given fast (within two seconds). The doses varied between 0.125 and 0.375 mg./kg. In the next two tests the drug was injected slowly (within two minutes). The doses were 0.25 and 0.5 mg./kg. body weight. Finally, in an attempt to maintain a constant degree of relaxation and to regulate the depth of muscular paralysis at will, a continuous drip of a solution containing 2 mg. per ml. in normal saline was set up. No medication other than oxygen by facemask was given before, during, and after the experiments.

Three members of our medical staff assisted in the tests. One administered oxygen from an anaesthetic machine and conducted the necessary artificial respiration. The second injected the drug and took pulse and blood-pressure readings. The third took electrocardiographic readings and kept the records. Electrocardiographic tracings were taken before, during, and after the experiments, with the exception of the first two, in which only the blood pressure, pulse, and respiratory rate were recorded.

Results

Experiment 1.—May 11, 1951. 10 mg. S.C.C. (0.125 mg./kg.) injected within two seconds. Effect:—After 30 seconds: onset of muscle weakness, double vision, ptosis, muscle-twitching of eyelids, masseter, arms, legs, and glutei. After 60 seconds: partial paralysis of respiratory muscles; difficulties in speaking; head and arms cannot be raised. After 90 seconds: effect decreasing; good abdominal relaxation. After 120 seconds: arms can be lifted; head still very heavy; respiration still slightly depressed; tone of abdominal muscles returning; speech almost normal; jaw relaxed; eye muscles still weak. After 180 seconds: effect completely worn off. During this experiment no artificial or assisted respiration was necessary. Blood pressure and pulse showed no changes.

Experiment 2.—May 11, 1951. 20 mg. S.C.C. (0.25 mg./kg.) injected within two seconds. Effect:—After 30 seconds: generalized fibrillary muscle-twitching in the same sequence as in the first experiment, lasting 5–10 seconds, followed by complete paralysis, including respiration; artificial respiration started. After 60 seconds: first movement of the diaphragm; assisted respiration kept up for approximately another 20 seconds. After 90 seconds: sufficient respiratory exchange with diaphragm only; intercostals and abdominal muscles still paralysed; jaw still completely relaxed; speaking impossible. After 120 seconds: arms can just be lifted; relaxation of abdomen decreasing; speech returning gradually; head cannot be raised. After 150 seconds: still unable to lift head; extremities can be moved freely; jaw still partially relaxed. After 180 seconds: head and eyelids still heavy; speech already distinct and clear. After 240 seconds: no subjective or objective effect left. In this experiment artificial respiration had to be maintained for about 50 seconds. Adequate relaxation for surgery lasted approximately two minutes. The test subject was conscious throughout. There were no side-effects, subjective or objective. Pulse and blood pressure remained almost unchanged.

Experiment 3.—May 12, 1951. 30 mg. S.C.C. (0.375 mg./kg.) injected within two seconds. Effect:—After 30 seconds: fibrillary muscle twitching as in the previous experiments; subjective effect more intensive and somewhat painful; 5 to 10 seconds later complete paralysis of all skeletal muscles; artificial respiration started. After 60 seconds: test subject still completely paralysed. After 90 seconds: diaphragm moving again, but no adequate respiratory exchange yet; assisted respiration for about 20 seconds, then discontinued; jaw and abdominal muscles still completely relaxed; speaking impossible. After 120 seconds: hands and feet can be moved; abdominal wall still soft; head cannot be raised; speech returning gradually. After 150 seconds: as in experiment 2. After 180 seconds: as in experiment 2. After 240 seconds: effect completely worn off. In this experiment artificial or assisted respiration had to be kept up for about 70 seconds. Muscular relaxation adequate for abdominal surgery lasted approximately two minutes. The test subject was conscious throughout. No side-effects, subjective or objective, were noted. The blood pressure remained at the original level throughout. Electrocardiograms showed practically no change in the heart action.

Experiment 4.—May 18, 1951. 20 mg. S.C.C. (0.25 mg./kg.) injected slowly within two minutes. Effect:—After 30 seconds (from start of injection): no effect. After 60 seconds: still no effect. After 90 seconds: eyelids becoming heavy; double vision developing; speaking difficult; extremities can be moved with a little difficulty; head cannot be lifted; jaw relaxed. After 120 seconds: effect less marked; speech clear; some muscle weakness still remaining. After 150 seconds: effect worn off. No muscle-twitching preceded the stage of paralysis this time. The respiratory exchange was adequate throughout, although the intercostal muscles were affected for a short period (20 to 30 seconds). The relaxation of the abdominal wall lasted less than one minute. No changes in pulse rate, blood pressure, and electrocardiogram could be recorded.

Experiment 5.—May 18, 1951. 40 mg. S.C.C. (0.5 mg./kg.) injected slowly within two minutes. Effect:—After 30 seconds (from start of injection): no effect. After 60 seconds: gradual paralysis just starting without preceding muscle-twitching; speech becoming heavy. After 90 seconds: total paralysis has been present for about 10 seconds, artificial respiration started. After 120 seconds: first movement of the diaphragm; ventilation insufficient; assisted respiration continued. After 150 seconds: extremities can be moved; jaw still relaxed; speech returning gradually; head cannot yet be lifted; respiratory exchange adequate with oxygen; assisted respiration discontinued. After 180 seconds: speech normal, distinct, and clear; some muscle weakness still present, particularly in the

neck. After 240 seconds (from beginning of injection): no objective or subjective effect apparent. In this experiment also the test subject remained conscious throughout. Although artificial and assisted respiration was necessary for about 50 seconds, pulse, blood pressure, and electrocardiogram remained essentially normal.

Experiment 6.—May 19, 1951. Continuous drip of a 0.2% solution in normal saline, 1 ml. (=20 drops) thus containing 2 mg. S.C.C. When running the drip at a rate of 50 drops a minute (=5 mg. S.C.C., or 0.06 mg./kg. body weight) the onset of muscle weakness was noted about two minutes after the start of the drip. Approximately one minute later diplopia developed, which was followed by marked ptosis and almost complete paralysis of the intercostals. Hands and feet could be moved, but the head could not be lifted. The speech was heavy, but could still be understood. No assisted respiration was necessary. The relaxation of the abdominal wall was comparable to stage III/2 ether anaesthesia. After five minutes the drip was turned off. One minute later the effect was decreasing rapidly, and another minute later it had almost completely worn off.

About 10 minutes later, when there was certainly no residual effect left, the drip was started anew at a rate of 100 drops a minute (=10 mg. S.C.C., or 0.125 mg./kg. body weight). The effect this time began about 90 seconds later with double vision, ptosis, general muscle weakness, and intercostal paralysis, followed about 30 seconds later by total paralysis, including the diaphragm. Artificial respiration was started and the speed of the drip slightly reduced (to approximately 80 drops a minute). An electrocardiogram showed no noticeable changes; the drip was stopped two minutes later. The total muscular paralysis lasted until 30 seconds after the drip had been discontinued. The diaphragmatic movements returned, and recovery in the usual order followed within about two to three minutes. The blood-pressure readings were around 125/80 mm. throughout, as in the previous experiments. The pulse rate slowed down from 74 to 68 a minute.

In these experiments the onset of the effect was slow and gradual, and the initial muscle-twitching was so slight that it was noted only by the test subject himself soon after the drip had been started at the fast rate.

Discussion

The aim of these experiments was to prove the specific action of S.C.C. on the skeletal muscle in man and its freedom from any undesirable side-effects. It could be shown that the muscular paralysis obtained with this drug was regular, quick in onset, and short in duration. In most experiments, particularly when larger dosages were injected rapidly, some fibrillary muscle-twitching, lasting only a few seconds, was observed. This was thought to be the manifestation of the commencing depolarization of the muscle membranes which finally results in greatly diminished response to stimulation of the motor nerves as well as the muscles proper. The mode of action of this compound thus seems to be similar to that of decamethonium.

No side-effects or after-effects were noted. There have been no attributable changes in pulse rate and blood pressure. The electrocardiogram was normal in all tracings. Consciousness was never lost, nor did the drug cause any degree of analgesia, as was proved by pin-prick tests.

Because of the small margin between the relaxing dose and the completely paralysing dose, and because of the rather painful muscle-twitching at the onset of its action, S.C.C. does not appear to be suitable for use in combination with local analgesics. It should be used only by anaesthetists, and the anaesthetic should be administered by means of an anaesthetic machine.

Following these observations in an unanaesthetized man, which proved the usefulness of the new drug as a muscle relaxant, clinical trials on patients under anaesthesia were started.

While this paper was being prepared preliminary reports on 17 cases (Brücke *et al.*, 1951) and 50 cases (Mayrhofer and Hassfurth, 1951) were published. Arnold *et al.* (1951) showed that the drug was also successful in mitigating the convulsions during electric convulsion therapy in psychiatric cases.

We have given up to ten times the paralyzing dose to patients under anaesthesia without seeing any side-effects attributable to the drug. Even with these excessive doses the effect did not last longer than 8 to 12 minutes (Mayrhofer and Hassfurth, 1951). We used S.C.C. for all types of operations, and for poor-risk patients as well, and have never encountered any difficulties. Very little thiopentone (up to 0.5 g.) was given for induction, and anaesthesia was maintained with nitrous oxide, pethidine, and, in some instances, an additional trace of ether. No cumulative effect was seen with any of the anaesthetics mentioned.

S.C.C. was particularly useful in facilitating endotracheal intubation, even in difficult patients in whom other curarizing agents had failed to produce adequate relaxation (Mayrhofer and Hassfurth, 1951). Several times it quickly and successfully relieved various degrees of laryngospasm, and in one case it terminated a rather marked bronchospasm following thiopentone induction (Mayrhofer and Hassfurth, 1951).

All patients were awake at the end of the operation; none showed any side-effects or after-effects. The surgeons were extremely pleased with the ideal relaxation for the closure of the abdominal wall; the anaesthetists were particularly satisfied with the complete absence of after-effects and the good respiratory exchange immediately after recovery from paralysis.

Recent reports indicate that a similar short-acting muscle relaxant has been synthesized (Tammelin and Löw, 1951) and tested (Thesleff, 1951) in Sweden. This drug, which has been used for a few months under the name of "L.T.1," is chemically the iodide of succinylcholine. We also used S.S.I. in some of our earlier trials, but since we were afraid of giving our patients too large dosages of iodine we switched to the equally active chloride, which has the additional advantage of being stable in solution.

Summary

Succinylcholine chloride, a new ultra-short-acting muscle relaxant, has been tested in self-experiments. Relaxation is rapid in onset, and the muscles are affected in the same sequence as with other curarizing agents. Its action is similar to that of decamethonium—namely, depolarization of the end-plate region of the skeletal muscles. It is destroyed in the body so rapidly—apparently by enzymatic hydrolysis—that no antidote is needed.

The resulting paralysis lasts from one to several minutes according to the dose. Recovery to full respiratory power occurs within three minutes after the first movement of the diaphragm, even following heavy dosage. Further doses may be given without the risk of dangerous cumulative effects. The drug appears to be free from side-effects or after-effects. Even with doses as high as several times the paralyzing dose no changes in circulation could be observed.

The results of our experiments suggest the following wide range of possible uses in clinical anaesthesia.

(1) *To provide relaxation for abdominal and thoracic surgery.*—Time and degree of relaxation wanted are better controlled with S.C.C. than with any other curarizing agent. Its short-lasting effect, however, may be a disadvantage at times when intermittent injection of the drug is not possible. For these cases the use of a continuous drip (0.1 or 0.2% in saline) is recommended.

(2) *To facilitate endotracheal intubation.*—The rapid onset of muscular relaxation and the absence of side-

effects render S.C.C. best suitable for this purpose. Yet care must be taken to avoid coughing or "bucking" on the tube owing to the rapid return to muscular power.

(3) *To overcome severe laryngeal spasm.*—Since S.C.C. takes effect within one minute from intravenous injection of the drug, a dose large enough to provide muscular paralysis will certainly cope with any form and degree of laryngeal spasm.

(4) *As an adjuvant in electric convulsion therapy.*—The short-lasting paralysis and the freedom from side-effects make S.C.C. the ideal drug for mitigating the muscle contractions during electric convulsion therapy.

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THE ULTRA-SHORT-ACTING RELAXANTS

BY

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The first English notice about an ultra-short-acting relaxant was a memorandum by Scurr (1951) describing a small trial of di-(β -ethylmethyl-ammonium-ethyl) succinate diiodide, a close relation of succinylcholine, and, like it and decamethonium, one of the depolarizing group of relaxants (Paton and Zaimis, 1950).

Succinylcholine iodide has been in regular use at the Karolinska Hospital at Stockholm since January, 1951; at the International Congress of Anaesthetists in September, 1951, von Dardel and Thesleff (1951a) reported on 1,000 cases. They are using it to the exclusion of all other relaxants, prolonging its action when necessary by the use of a continuous infusion. One of us (H. R.) saw it in use at Stockholm, and a supply was kindly made available for clinical trial at Cambridge. This report is based on personal use of succinylcholine in 250 cases.

Use in Single Doses

There are now several succinylcholine derivatives in use. It seems probable that doses of all of them containing equal quantities of the active radical have identical effects. The Swedish product, "celocurine," is succinylcholine