THE NEUROMUSCULAR ACTIVITY OF SUCCINYLMONOCHOLINE IODIDE IN ANAESTHETIZED MAN

BY

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It was reported by Whittaker and Wijesundera (1952) that succinylcholine (succinylidicholine ; SDC) is hydrolysed by horse serum cholinesterase in two steps: first one molecule of choline is split off at a fairly rapid rate from the SDC molecule and then the resulting succinylmonocholine (SMC) is hydrolysed more slowly to succinic acid and choline. Subsequently, Tsuji and Foldes (1953) and Lehmann and Silk (1953) have shown that SDC is hydrolysed in the same manner by human plasma and concentrated human plasma cholinesterase respectively. Foldes and Tsuji (1953) and Foldes (1953) also reported that SMC-I in doses of 2 to 2.5 mg. per kg. caused complete neuromuscular block for about 10 to 15 minutes and partial block for about 20 to 30 minutes in the sciatic-gastrocnemius preparations of cats anaesthetized with pentobarbitone. Lehmann and Silk (1953) found that in rabbits SMC (active cation) in doses of 2.5 mg. per kg. and 3.5 mg. per kg. produced paralysis without apnoea for 150 and 550 seconds respectively. Doses higher than 5 mg. per kg. regularly caused respiratory paralysis in rabbits. Ellis *et al.* (1953) investigated the neuromuscular effects of SMC-I in several species and found that on a molar basis its activity varied from 1/24 to 1/62 of that of SDC-Cl₂. They also found that in mice SMC-I is 1/14 as toxic as SDC-Cl₂.

Present Investigation

In view of the fact that SDC-Cl₂ is being used with increasing frequency for the production of muscular relaxation for operative procedures, and that occasionally as much as 12 mg./min. of SDC-Cl₂ has been administered to patients for prolonged periods (Bourne *et al.*, 1952), it seemed worth while to investigate the muscle-relaxant properties of SMC-I in humans to find out whether or not the SMC concentrations resulting from the hydrolysis of the relatively large quantities of SDC-Cl₂ administered to patients in the course of long operative procedures might have any effect on neuromuscular conduction. Since it is not possible to predict from the effects of muscle relaxants observed in one species the effects to be expected on another species (Paton and Zaimis, 1950 ; Unna *et al.*, 1950) such information could be obtained only by observing the effect of the administration of SMC-I on human volunteers or on patients requiring muscular relaxation for various operative procedures. We chose the latter course.

At first SMC-I was administered in doses of 1 mg. per kg. to patients anaesthetized with combinations of thiopentone sodium/N₂O-O₂/pethidine according to a previously described technique (Foldes *et al.*, 1952). This dose of SMC-I had no discernible neuromuscular effect. Therefore the initial dose of SMC-I was gradually increased in subsequent patients to 5 to 7 mg. per kg. body weight. With this dosage, muscular relaxation developed in three to five minutes and lasted

from eight to twelve minutes. This relaxation could be maintained by the repeated intravenous injections of 3 to 4 mg. per kg. of SMC-I at intervals of eight to twelve minutes. The resulting muscular relaxation was adequate for the performance of various intra-abdominal operations. The respiratory depth of the patients was hardly affected at times when good abdominal relaxation was present. It has been the impression of the anaesthetists and surgeons that increased diaphragmatic activity compensated for the intercostal paralysis in the maintenance of adequate respiratory depth.

The jaw musculature and the vocal cords were not as well relaxed even after 7 mg. per kg. as after the use of some other neuromuscular blocking agents, but the patients could be intubated without major difficulty.

It was observed that SMC-I markedly potentiated the neuromuscular blocking activity of subsequent doses of SDC-Cl₂ at a time when the patients had apparently recovered from the effects of the former. In a 22-year-old woman weighing 75 kg. the injection of 20 mg. of SDC-Cl₂ produced in 40 seconds slight respiratory depression for 225 seconds. Seven minutes after the intravenous administration of 350 mg. of SMC-I, an identical 20-mg. dose of SDC-Cl₂ produced in 25 seconds respiratory arrest for 270 seconds, and some respiratory depression for an additional, 210 seconds.

Owing to the limited supply of SMC-I at our disposal, it was used for the production of muscular relaxation in only 10 patients. The operative procedures included 3 appendectomies, 4 cholecystectomies, 2 hysterectomies, and 1 exploratory laparotomy. Satisfactory abdominal relaxation was obtained in all patients without the development of respiratory arrest or more than a moderate degree of respiratory depression. The pulse and blood pressure of the patients remained remarkably constant. The muscular relaxation had a tendency to wear off abruptly unless a fractional dose was administered at the first sign of its fading effect. In general, the relaxation obtained with SMC-I resembled that obtained with decamethonium.

No prolonged post-operative respiratory depression was observed in any patient in this small series. Respirations became normal within 8 to 12 minutes after the administration of the last fractional dose in all instances.

Muscular twitchings occasionally seen with decamethonium and more frequently with SDC-Cl₂ were not observed with the use of SMC-I.

The urinary excretion of SMC-I was followed in two patients. Urine was collected during and 15 minutes after the administration of a relaxant dose of SMC-I. The patients excreted 11.8% and 14.5% of the administered SMC-I during this period. In contrast to this less than an average of 3% of the administered SDC-Cl₂ could be recovered from patients under identical circumstances (Foldes and Norton, to be published).

Discussion

The neuromuscular effect of SMC-I represents a transition between that of decamethonium and SDC-Cl₂. The onset and duration of the neuromuscular blockade with SMC-I resembles that seen with the use of decamethonium. On the other hand, its elimination from the body is similar to that of SDC-Cl₂. Whereas decamethonium can be recovered almost quantitatively unchanged in the urine after its administration (Paton and Zaimis, 1952), most of the SMC-I is hydrolysed in the body to succinic acid and choline. However, since the hydrolysis of SMC-I by the plasma cholinesterase is much slower than that of SDC-Cl₂, urinary excretion plays a greater part in the elimination of SMC-I than is the case with SDC-Cl₂.

The findings presented indicate that in the average patient 0.3 to 0.4 mg./kg./min. of SMC-I gave adequate muscular relaxation without the development of undue respiratory depression. It has been our experience that the administration of 0.05 to 0.15 mg./kg./min. of SDC-Cl₂ was necessary in a large group of patients for the production of good

muscular relaxation. Since the ratio of the molecular weights of SMC-I and SDC-Cl₂ is about 0.8, the hydrolysis of 0.05 to 0.15 mg. of SDC-Cl₂ will produce the equivalent of 0.04 to 0.12 mg. of SMC-I. This dose of SMC-I has little or no effect on neuromuscular conduction in patients whose ability to hydrolyse and excrete SMC-I is unimpaired. However, in patients with low cholinesterase activity, especially if their kidney function is also diminished, the administration of relatively large doses of SDC-Cl₂ for prolonged periods might lead to the accumulation of SMC in sufficiently high concentrations to potentiate the neuromuscular action of the unhydrolysed SDC-Cl₂. Such a set of circumstances can arise if muscular relaxation is maintained in patients with low plasma cholinesterase activity with SDC-Cl₂ by the "apnoeic technique."

With this technique the administration of SDC-Cl₂ is carried to a point where the patient's voluntary respiratory movements are completely abolished and gas exchange is maintained by manual compression of the breathing-bag of the anaesthesia machine. Since the administration of SDC-Cl₂ in amounts many times higher than the apnoeic dose has no discernible effect on blood pressure, pulse rate, or any other physiological process, there is no sign that would indicate whether just enough SDC-Cl₂ is administered for production of apnoea or whether large doses of SDC-Cl₂ accumulate in the organism. If the latter of the two possibilities occurs in patients with low plasma cholinesterase activity and with decreased urinary excretion, prolonged post-operative respiratory depression will result. Since adequate muscular relaxation can be obtained with SDC by utilizing the difference in sensitivity to this agent between the diaphragm and intercostals, there seldom is a need for the application of the apnoeic technique.

It is unlikely that SMC plays a similar part in the prolonged respiratory depression occasionally observed after the administration of a single large dose of SDC-Cl₂ (Hewer, 1952; Love, 1952; Harper, 1952; and others). The hydrolysis of as large a dose as 100 mg. of SDC-Cl₂ will yield only about the equivalent of 80 mg. of SMC-I, and this dose is not likely to have any neuromuscular blocking effect. The prolonged apnoea under such circumstances is caused either by an exceptionally low plasma cholinesterase activity of the patient or by the combination of acapnia due to too energetic controlled respiration, and reflex breath-holding arising from the stimulating effect of the endotracheal tube on the larynx and trachea in the patient in whom the level of general anaesthesia was allowed to become too light.

Owing to the relatively large doses in which SMC-I has to be administered, the less satisfactory relaxation obtained, and the lack of rapid and easy controllability of its neuromuscular effect, SMC-I does not seem to offer any advantages in comparison with other available muscle relaxants, especially SDC-Cl₂.

Summary

In man SMC-I in doses of 5-7 mg. per kg. produced in three to five minutes muscular relaxation of 8 to 12 minutes' duration.

Muscular relaxation could be maintained by repeated intravenous injections of SMC-I in doses of 3-5 mg. per kg. 8 to 12 minutes apart.

These doses of SMC-I caused little respiratory depression.

The administration of SMC-I markedly potentiated the neuromuscular action of subsequent doses of SDC-Cl₂.

The possible role of the accumulation of SMC in the development of prolonged apnoea after the use of SDC-Cl₂ is discussed.

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BACTERIAL ENDOCARDITIS DUE TO CHROMOBACTERIUM PRODIGIOSUM

REPORT OF A CASE

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Chromobacterium prodigiosum (*Serratia marcescens*) is usually regarded as non-pathogenic for man, and Wilson and Miles (1946) were unable to quote any indubitable report to the contrary. In 1952, however, Patterson, Banister, and Knight described a case of septicaemia due to this organism, and reviewed the literature concerning human infections with members of the *Chromobacterium* group. They quoted 21 records of infection by *Chr. prodigiosum*, including their own, only one of which was a case of endocarditis (Wheat, Zuckerman, and Rantz, 1951).

Case Report

An African man aged 38 was admitted to the Gold Coast Hospital, Accra, on April 30, 1953, after a month's sickness; this began with fever and headaches, accompanied by rigors. After taking mepacrine and "phensic" tablets he was able to continue his work as an omnibus inspector. About a week before admission he had had further headaches with fever and pain in the neck. He attended the out-patient department on April 25, when a blood film proved negative for malarial parasites, but the urine was found to contain albumin. He was given an injection of sulphasolucine, 5 ml., and another of quinine, 10 gr. (0.65 g.), both intramuscularly, as well as 2 ml. of mersalyl. He was subsequently referred to A. J. H. and was admitted for investigation.

On admission he complained of feverishness and pain in the umbilical region. His temperature was 101° F. (38.3° C.). A blood film was again negative for malarial parasites and there was a heavy cloud of albumin in the urine. He was systematically examined on May 1. It was noticed that he had lost weight. He was obviously a sick man, but in no way distressed. No rash was found on his skin and his temperature was 104.2° F. (40.1° C.). His bowels had been open daily and the stools were semi-solid. His tongue was moist and a little furred. Except for the complaint of pain in the umbilical region no abnormality was found in the alimentary system. The chest was clear and the sinuses appeared to be normal; the respiration rate was 30 a minute. The cardiovascular system showed nothing abnormal beyond a pulse of 120 a minute. The patient complained of a frontal headache, which was worse when the fever was high in the evenings, but a clinical examination