1954

Succinylcholine: ultra-short-acting muscle relaxant

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Submitted in Partial Fulfillment for the Degree of Doctor of Medicine

College of Medicine, University of Nebraska

March 24, 1954

Omaha, Nebraska

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INTRODUCTION AND HISTORY

Succinylcholine was first mentioned by Hunt and Taveau (1) in 1911 and later by LeHeux (2) in 1921. They do not report any complete directions for the synthesis but the compound was isolated as a chloroplatinate. Glick (3) in 1941 showed that it was readily hydrolyzed both by the esterase of horse-serum and by alkali. In 1949 Fusco et al (4) made a thorough investigation of choline esters with neuromuscular blocking effect and in their papers several principles of synthesis of the compounds were given, among them succinylcholine. In 1950 Walker (5) synthesized succinylcholine and reported more complete values of analysis and yield.

Shortly after the discovery of decamethonium by Barlow and Ing (6) in 1948 and Paton and Zaimis (7) in 1948, Buttle and Zaimis (8) and Phillips (9) in 1949 and Walker (5) in 1950, in England, Bovet et al (10) in Rome, and Castillo and de Beer (11) in 1950, in Tuckahoe, N.Y., showed independently that succinylcholine possessed high neuromuscular blocking activity. In spite of its relative high potency, succinylcholine was not developed for clinical purposes by any of these groups of investigators. Bovet et al (10) preferred the corresponding bisethiodide (succinylcholine iodide), which he considered might lack

some minor side-effects anticipated from succinylcholine chloride itself; and in London, and perhaps in the U.S.A., succinylcholine chloride was not pursued further at the time, because it was thought to be too short-acting.

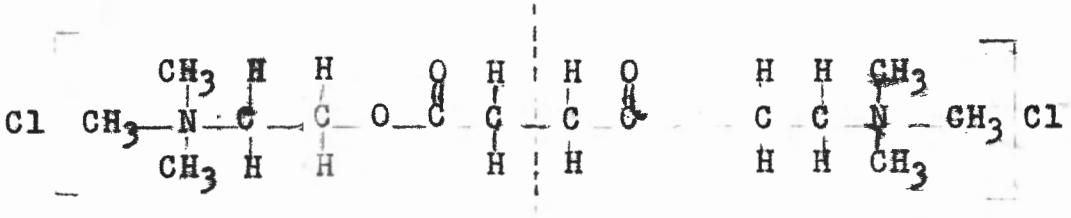
The need for a really short-acting relaxant was too insistent, however, to allow succinylcholine to remain long unused. The possibility of its employment was explored independently in Sweden (Thesleff (12) (13) in 1951, Thesleff et al (14) in 1951), in Austria (Brucke et al (15) in 1951) and in England (Bourne et al (16) in 1952). All these groups found that the side-effects of succinylcholine feared by Bovet et al (10) were absent or negligible in man, and that the effect of succinylcholine lasted for a much shorter time than the considerably more potent decamethonium. Here is a concrete example of the exchange of potency for the more desirable property of brief action.

Thesleff et al (14) in 1952 published one of the first reports on an extensive series of cases on the use of succinylcholine. It was used by them in 1,000 cases since January, 1951, in all age groups except infants, in all risk groups.

Brucke et al (15) published the first report in 1951 of the use of succinylcholine on an anesthetized patient.

CHEMISTRY

Little et al (17) state, " Succinylcholine, or diacetylcholine, is in fact two molecules of acetylcholine linked together at the alpha-methyl groups in such a way that there are 10 atoms interposed between the two quaternary nitrogens previously hypothecated (6) as being necessary for neuromuscular blocking activity, thus:



Paton (18) states, " Quaternary nitrogen provides far the richest quarry for neuromuscular blocking agents. In those compounds, the terminal groups should remain acetylated, as they are in acetylcholine. The theory that a distance corresponding to 8-12 carbon atoms between two quaternary groups favors neuromuscular activity has proved successful. There is no evident reason for this. A bare aliphatic scaffolding, such as in decamethonium, seems to favor depolarizing action whereas a well-upholstered molecule (such as d-Tubocurarine) is more likely to be competitive. All the drugs which compete with or mimic acetylcholine at all closely, resemble it in chemical structure.

This has important consequences for the way such drugs are handled by the body and for their side-effects."

Barlow and Ing (6) and Paton and Zaimis (7) in 1948 discovered the powerful curare-like activity in a series of straight-chained polymethylene bis-quaternary ammonium salts, and Phillips (9), stimulated by their work, sought to produce compounds of similar activity by duplicating the chain length. He found them to be of 10 atoms distance between the quaternary nitrogens. The first compound he made, the bis-diethyl-aminoethyl succinate bismethiodide, has 10 atoms interposed between the quaternary salt groups, and showed a curariform activity equal in intensity to that of d-Tubocurarine as determined by its ability to block neuromuscular transmission in the cat, but the effect was of much shorter duration than that produced by d-Tubocurarine. This shorter duration of action was attributed to the action of choline esterases based on the similarity between this substance and two molecules of acetylcholine coupled at the alpha-carbon.

The compound originally used was the iodide of the dicholine ester of succinic acid, succinylcholine di-iodide. Because of the fear of administering too great an amount of iodide to the patient, the chloride has been used almost exclusively. The physical properties are a great deal alike, however (Low and Tammelin (19)).

Low and Tammelin (19) purified the substance by recrystallization. It is more commonly known now as the dichloride. It is a white solid which crystallizes with two molecules of water. The dihydrate so formed has a melting point of 157 degrees Centigrade. The preparation is readily soluble in water to form a stable and slightly acid solution, but it is rapidly hydrolyzed by alkaline solutions, a warning that it must not be mixed with pentothal (Castillo and de Beer (10)).

Collier states, "The idea that succinylcholine is a very unstable compound arises through its rapid disappearance in the body and also its rapid destruction when mixed with thiopentone solution, which is alkaline. Succinylcholine, on the contrary, forms a reasonably stable solution in saline." He found the solution was not detectably altered after standing for 21 days at room temperature.

Britton and Volpitto (21) performed studies of succinylcholine stability after finding that when the solution was mixed with barbital solutions, the succinylcholine was rendered ineffective. They found that succinylcholine was destroyed almost completely by a pH over 11.0, and little at all below 9.5. By increasing the proportion of hexobarbital to succinylcholine, they could delay this destruction 5 or 10 minutes.

Lehmann and Silk state, "Whittaker and Wijesundera (23) in 1951 described work done with a highly concentrated horse pseudocholinesterase (33,000 units/ml.), confirming that, in the enzymatic breakdown of succinyldicholine, first succinylmonocholine was formed, but this was an intermediate which was subsequently hydrolyzed to succinic acid and choline, thus:

succinyldicholine → succinylmonocholine + choline

succinylmonocholine → succinic acid + choline."

Lehmann and Silk (22) found the same to occur with human serum, and when they used similar concentrations (succinyldicholine 1.1, succinylmonocholine 0.7 mg active cation/ml.) could show that succinyldicholine was at first hydrolyzed 4-6 times as fast as succinylmonocholine, but that at concentrations between 40% and 60%, the speed slowed and became identical with that of hydrolysis of pure succinylmonocholine. Whereas succinylmonocholine resembles succinyldicholine in its response to pseudocholinesterase, as a substrate of the true cholinesterase of the red cells it occupies a position midway between acetylcholine and succinylcholine. Succinylmonocholine, like acetylcholine and unlike succinyldicholine, is hydrolized by true cholinesterase at low substrate concentration. It resembles succinyldicholine in inhibiting acetylcholine hydrolysis by the true cholinesterase, but whereas

succinyldicholine is still effective at very low concentration (Evans et al (24), 1952), succinylmonocholine inhibits only at the high levels at which acetylcholine itself becomes an inhibitor. Lehmann and Silk (22) further state, "It has hitherto been impossible to allot to pseudocholinesterase a function in life, because it could be removed by specific inhibitors in vivo without any ill effects. There are at least four compounds now which poison the true cholinesterase and are destroyed by the pseudocholinesterase: acetylcholine and succinylmonocholine in high concentrations; succinyldicholine and suxemethonium at high and low concentrations."

Foldes and Tsuji (25) and Tsuji and Foldes (26) found in in vitro studies with succinylcholine dichloride that the hydrolysis of this compound by human plasma cholinesterase stops or slows down markedly after one choline molecule had been split off. To obtain further information on the probable fate of succinylcholine in plasma, they observed the enzymatic hydrolysis of the half-ester and found that the enzymatic hydrolysis of the half-ester was 6-7 times slower than that of succinylcholine dichloride.

PHARMACOLOGY

Foldes et al (27) write, "It is generally accepted that the ideal muscle relaxant should have specificity and rapid onset of action, readily controllable intensity, wide margin between muscular relaxation and respiratory arrest and rapid and complete recovery, without the cessation of its administration. The agents employed hitherto (to succinylcholine) have fallen far short of the above requirements." Little et al (17) doubt the fulfillment of all these criteria by any one drug, but believe succinylcholine comes close to that ideal on a number of different counts, mainly because a total relaxant dose is fully dissipated within two or three minutes.

Type of Action

Paton (18) described two types of neuromuscular block: 1) Competitive - such as d-Tubocurarine - lessens the effectiveness of acetylcholine at the end-plate. It is supposed that these drugs acting in this way (almost invariably salts of quaternary nitrogen) are sufficiently like acetylcholine to have some affinity for its receptor sites but sufficiently unlike to be incapable of initiating the process of depolarization. They thus 'compete' for receptor sites with acetylcholine, and so render a given quantity of the latter less effective than normally. The end-

plate potential aroused thus comes to fall short of the amount needed to activate the adjoining muscle membrane. Their action is precisely analogous to many other pharmacological antagonisms, such as that of hexamethonium at the ganglionic synapse, or of antihistamines against histamine; 2) Depolarizing - such as decamethonium bromide and succinylcholine - these are drugs having a closer relationship to acetylcholine so that they can actually initiate the depolarization process. Decamethonium can depolarize the motor end-plate in doses almost as small as those in which acetylcholine act, but, unlike acetylcholine, the compound cannot be hydrolyzed, so that the depolarization produced may last not for milliseconds, but for minutes or even hours.

It is suggested that the action of succinylcholine might be indirectly through the inactivation of the cholinesterase, but Paton (18) concludes, "There is no evidence for this. It is known to depolarize muscle directly; for instance, a dose of two micrograms injected into a cat's tibialis produced a substantial reduction of membrane potential, although in the same preparation 0.5 mg neostigmine had no depolarizing action. It is in any case only a weak anti-cholinesterase."

Collier (20) believes there is no doubt that succinylcholine has a depolarizing action, that is to say, it in-

duces a state of excitation that prevents further impulses being transmitted. Two views as to how this excitation arises have been suggested: one is that succinylcholine acts, like decamethonium, directly on the end-plate by mimicking the action of acetylcholine. This view rests on measurement by Paton and Dias (28) of the electrical potential of the motor end-plate in relation to that of the rest of the muscle. Such measurement shows that very small quantities of succinylcholine excite the end-plate, although relatively enormous quantities of neostigmine fail to do so. Another view, that succinylcholine acts indirectly, by inhibiting the destruction of acetylcholine has been put forward by Evans et al (24); and Hall et al (29) advance further experimental support, which is however based on work in dogs. Collier (20) finds several difficulties in accepting this: 1) it is not easily reconciled with the report of Paton and Dias (28), 2) it seems unlikely from the figures of Evans et al (24) and from other evidence that the concentration of succinylcholine effective in paralyzing the human body are sufficient appreciably to inhibit cholinesterase, and 3) twitches due to intravenous injection of succinylcholine in man appear without any latency, other than the circulation time, even in resting muscles.

Evans et al (24) believe that the target of the drug

is the acetylcholine of the nerve-muscle end-plates because the longest response seen so far is that case when neostigmine was given and the patient did not recover for three hours. (Harper (30)). Orton (31) believes the action of succinylcholine is like that of excess acetylcholine, such as is produced in a normal person by administration of neostigmine. Britton and Volpitto (21) noted that the occasional twitching observed after the administration of succinylcholine could also be seen after the use of syncurine, and also after the injection of acetylcholine, concluding that this phenomenon was caused by the depolarization of the neuromuscular membrane, which in turn initiated the action potential that results in muscular contractions. Castillo and de Beer (11) state, "The site of action of succinylcholine was established as being at the neuromuscular junction since this drug inhibits the contractions produced in the gastrocnemius of the atropinized cat by the rapid injection of acetylcholine into the femoral artery."

Actions in Man

Thesleff (32) states that, "In the clinical employment of curare and curare-like preparations there have been a number of undesirable complications, the foremost of these being a fall in blood pressure, bronchospasm, salivation and urticaria, and that the cause is attributed

to the release of histamine and the paralysis of the autonomic ganglia to which various muscle relaxing agents can give rise." In his experience with 1,000 cases (Thesleff (13) and Thesleff et al (14)) he has found succinylcholine to cause none of the above complications. He believed it important, however, to be able clinically to exclude an influence on blood pressure and cardiac rate as well as on histamine liberation. He carried out his experiments directly on man because he believed it difficult to draw conclusions regarding the action of muscle relaxing agents in man solely from results in animal experiments. In his experiments no substantial changes in blood pressure, heart rate or rythm were noted.

In experiments on unanesthetized patients, Thesleff (32) sought to determine by EEG the central effect of succinylcholine. In three instances he found EEG evidence of physical and emotional distress occurring 45-60 seconds after the injection. Severe diplopia, followed by paralysis of the pharynx and heaviness of the legs with difficult movements were noted in all patients. He found that patients also complained of a tightness over the chest accompanied by apprehension and a feeling of distress and cold sweat. After about two minutes the paralysis disappeared and a few minutes later the subject was able to get up and move about freely. He mentioned that some of

the patients felt twitchings just prior to paralysis but there was no particular discomfort or pain associated. The subjects sensorium remained clear. A slight weakness and unsteadiness generally persisted for up to one hour, but work could be carried out as usual. He found that all patients reported a diffuse pain in the muscles of the jaw and calf on the same day.

Bourne et al (16) also give an account of the sequence of events following injection of succinylcholine: "The first visible effects of injection of succinylcholine were diffuse uncoordinated contractions of muscle bundles and groups. These were seen in adults in 12-15 seconds and in children as soon as seven seconds after injection. In a conscious volunteer these contractions were painful, a fact which contraindicates the use of succinylcholine unless coma has been previously induced; and, since these contractions come on more quickly than thiopentone takes effect, the two drugs should not be mixed in the same syringe. The contractions caused by succinylcholine lasted 15-20 seconds, and their disappearance indicated the onset of paralysis. In the great majority of these patients, this paralysis lasted 2-6 minutes; muscle power than began to return and was normal in a further 3-4 minutes. Smaller doses than 1/100

of the pound-weight in ml. produced a more transient, and larger doses longer, paralysis. Effective doses always caused respiratory arrest. This was counteracted in short procedures by inflating the lungs with oxygen. During longer operations, artificial respiration was continued with the nitrous oxide/oxygen mixture of 75/25 respectively. Excessive artificial respiration, which would lead to acapnea, was avoided. In almost all cases the duration of action of succinylcholine is between 2-4 minutes, but the occasional prolonged action led observers to investigate the cause and thus better understand the mechanism of its rapid action."

Lehmann and Silk[22] state, "The short action of succinylcholine depends on its rapid destruction by serum-cholinesterase, thus the injection of a powerful inhibitor of this enzyme such as neostigmine would delay recovery almost indefinitely in a patient who already had a low serum-content of this enzyme. There may well be other mechanisms of succinylcholine removal; in the absence of the enzyme defense mechanism, excretion by the kidneys may play a part; but there seems to be no reason at present to consider anything other than serum-cholinesterase activity. To produce dramatic delay in recovery, the enzyme level must obviously be very low, and Callaway et al

(33) have shown that there is little chance of encountering such cases in an average sample of the population. If patients likely to have a low serum-cholinesterase (those with liver disease, anemia, malnutrition, post-irradiation, and possibly polyphosphate poisoning) are excluded from succinylcholine treatment, and if it is realized that neostigmine is contraindicated after the drug has been given, the use of succinylcholine should be quite safe."

Durrans (34) believes the fit younger patients require more of the drug than older patients, and the response and recovery time varies very little with either.

Little et al (17) report that succinylcholine is hydrolyzed by both the 'pseudo'-cholinesterase of the plasma and the 'true'-cholinesterase of the red cells, but more rapidly by the former, therefore concluding that the duration of action of succinylcholine depends upon the speed of its removal by 'pseudo'-cholinesterase.

Harper (30) remarks of the variation of the rate of hydrolysis of succinylcholine in man and animal, and between the sera of different individuals.

It has been known since 1949 that succinylcholine is destroyed by rabbit cholinesterase (Bovet et al (10)). With this information Evans et al (24) studied the enzym-

ic hydrolysis of succinylcholine in vitro and measured the serum-esterase level in four people who showed a normal reaction to the drug, and in two patients whose response was prolonged. They found that succinylcholine is metabolized by the 'pseudo'-cholinesterase of the plasma, but at a slower rate than acetylcholine; and succinylcholine is a competitive inhibitor of acetylcholine hydrolysis by both the true and the 'pseudo'-cholinesterases; but, of the two, the true esterase is more strongly inhibited. In the two patients who responded to the standard dose of succinylcholine with a paralysis of 20 and 21 minutes, they found the 'pseudo'-cholinesterase levels to be very low, both being 12 units (Callaway et al (33)), and the levels of the four who responded normally to succinylcholine to be from 55-98 units.

Comparison With Other Relaxants

Paton (35) states, "Acetylcholine is involved in transmission of nervous effects at three sites outside the CNS: 1) the parasympathetic endings, and the sweat glands, 2) the ganglia, and 3) the neuromuscular junction. A relationship between acetylcholine and the various relaxant drugs may show itself in one of three ways: a drug may 1) imitate acetylcholine, 2) competitively block it, and 3) inhibit the enzyme destroying it. We have thus nine types of action centred around acetylcholine;

a drug may mimic, inhibit or preserve the transmitter at any of three synapses. All these actions are liable to be displayed in widely different proportions by different relaxants. It becomes necessary, therefore, in studying the properties of neuromuscular blocking agents, to be prepared for such additional actions. The ganglion-stimulating action of succinylcholine, the ganglion-blocking action of d-Tubocurarine, and the anti-esterase action of Mytolon are the most important examples in the present context."

The comparative actions of the different muscle relaxants were first studied in animal experiments, on the cat, dog and rabbit.

Mayrhofer (36) studied the effects of succinylcholine on animals as well as himself, in comparison to other similar compounds. He found that succinylcholine has a nicotine-like stimulating effect as well as muscular paralysis, the strongest neuromuscular blocking effect, and the weakest stimulating effect to the autonomic ganglia. There was no increase in blood pressure in his experiments with cats under artificial respiration, until at least several hundred times the paralyzing dose had been given.

Mayrhofer (36) states, "Since the paralyzing effect of succinylcholine on the skeletal muscle is due to depolarization of the end-plate region, its action is not

counter-acted by anti-cholinesterases as is the case with d-Tubocurarine and flaxedil. It may even be prolonged to some extent. No antidote is felt needed, since its action is over in a matter of minutes." Bourne et al (16) state neostigmine is worse than useless and is contraindicated as an antidote to succinylcholine, while it is very useful in counter-acting the action of d-Tubocurarine and gallamine.

"In studying the actions of succinylcholine it resembles decamethonium but differs from d-Tubocurarine," Bourne et al (16) state. Buttle and Zaimis (8) studied the comparative actions of the relaxants on the amphibian muscle, and found that both succinylcholine and decamethonium caused contracture, while d-Tubocurarine did not. Bourne et al (16) found that, as with decamethonium, antagonism exists between succinylcholine and curare-like drugs. Thus succinylcholine administration to the cat during recovery from true curarization was found to hasten that recovery. Though succinylcholine resembles decamethonium in its action, it differs from decamethonium in being destroyed by cholinesterases.

Barlow and Ing (6), in studying actions of a C10 member of bis-quaternary salts, found it to have an action about three times as potent as d-Tubocurarine. Castillo

and de Beer (11) found succinylcholine to have a strength of paralysis equal in intensity to d-Tubocurarine in the rabbit, and 1/3 as potent in mice. Paton and Zaimis (7) found that the comparison of potency in relation to d-Tubocurarine varied with the test object, demonstrating the importance of pharmacological testing on different subjects when searching for substitutes for d-Tubocurarine. They found that the main difference between the C10 derivative and d-Tubocurarine was that the former has a relative sparing action on respiration. They used the rabbit head-drop test for curare-like activity, finding that 0.11 mg/kg of the C10 derivative was required to produce head-drop, while 0.25 mg/kg of d-Tubocurarine was required. Wnuck et al (37) compared the doses of relaxants required to abolish the twitch response of gastrocnemius of the cat to indirect stimulation; 0.1 mg/kg of d-Tubocurarine was required, 0.015 mg/kg of decamethonium bromide was required, and 0.075-0.10 mg/kg of succinylcholine was required. Foldes et al (27) were impressed with the good muscular relaxation that could be obtained with less respiratory depression with succinylcholine as compared with the other relaxants. They observed further that respiratory depression occurred in 12-21% of the patients after the use of other muscular relaxants, and was not observed in any of the patients after the use

of succinylcholine.

Castillo and de Beer (11) found in experiments on the neuromuscular blocking action of succinylcholine that the rapid intravenous injection in cats caused a prompt and complete block, but the effect was of much shorter duration than the incomplete blocks produced by either C10 or d-Tubocurarine. Wnuck et al (37) found the duration of action of d-Tubocurarine and decamethonium varied from 20-45 minutes, while that of succinylcholine varied from 3-7 minutes. D-Tubocurarine was observed to have a cumulative action, while succinylcholine did not, and the onset of paralysis of d-Tubocurarine varies from 3-8 minutes, while the onset of action of succinylcholine is in about ½ minute.

Ellis et al (38) studied the central respiratory depression of succinylcholine in the phrenic-nerve-diaphragm and sciatic nerve-gastrocnemius preparations of the cat, with restoration of spontaneous respiration by lobeline. They compared this action to that of d-Tubocurarine and decamethonium bromide. They found that, following succinylcholine, recovery occurred without the use of a specific antagonist to the succinylcholine. They state, "This fact that succinylcholine seems to be less prone to cause central respiratory depression may be further emphasized by the difficulty in consistently producing a prolonged

arrest of spontaneous respiration with this compound. With succinylcholine in doses of 0.2 mg/kg, only 3 of 11 responses were accompanied by a protracted respiratory failure. In one of these lobeline in a dosage of 0.2 mg/kg promptly relieved the depression. In the other two the spontaneous respiratory movements returned within about 2 minutes after the return of myoneural transmission. This is in direct contrast to decamethonium in which evidence of central depression was obtained in 7 of 10 responses, and to d-Tubocurarine, in which 3 of 6 showed central depression."

Thesleff (32), in his studies of comparison of the relaxants, emphasized the effects of them on the autonomic ganglia. It required 130-140 mg/kg of succinylcholine or 650-700 times the muscle-paralyzing dose to block the action potential in the ganglion, while 0.3-1.0 mg/kg of d-Tubocurarine or 1-3 times the muscle paralyzing dose, was required. It required 13-14 mg/kg or 25-30 times the muscle-paralyzing dose of flaxedil, and 2-3 mg/kg or 65-100 times the muscle-paralyzing dose of decamethonium. Doses of succinylcholine up to 30mg/kg did not produce bronchospasm. In concentrations of up to 50 mg/kg, succinylcholine did not affect the isolated ileum of the guineau-pig, rabbit or cat. The drug was not observed to cause any perceptible muscular paralysis in full-term

foetuses of pregnant rabbits, and the injection of 20-50 mg substance into the uterine arteries in 3 gravid women at the time of caeserian section, resulted in no paralysis of the foetuses.

In the study of histamine reaction, Thesleff (32) compared d-Tubocurarine and succinylcholine with intracutaneous injections. In all cases with the injection of d-Tubocurarine there was a severe irritation and wheel while with succinylcholine there was little or none. Thus compared with d-Tubocurarine, succinylcholine causes little or no histamine liberation.

Toxicity

Bourne et al (16) studied the toxicity of repeated doses of succinylcholine in rabbits. Rabbits were given daily intravenous doses of 100 micrograms/kg, which was enough to paralyze all of them, but to kill none. They were given these daily doses for 5 successive days. The animals were subsequently kept under observation for eight weeks without any delayed toxic effects being manifest. This freedom from toxicity has also been demonstrated by Bovet et al (10) in 1951. They found that dogs whose respirations were maintained in an iron lung could tolerate doses of succinylcholine 450 times the paralyzing dose. Paton and Zaimis (7) in their toxicity studies of the C10 derivative on rabbits and cats, found they were able to receive curarizing doses of the C10 compound daily

for six weeks without change in type or degree of the paralysis, or deterioration in the health of the animal. Thus, the freedom from toxicity of succinylcholine compares with that of decamethonium bromide.

DOSAGE AND ADMINISTRATION

How Supplied

Succinylcholine ('Anectine', Burroughs Wellcome; 'Quellicin', Abbott; 'Sucostrin', Squibb) is supplied in 10 cc. multiple dose vials, 20 mg/cc; 10 cc ampuls, 50 mg/cc; and ampuls of 100 mg dry substance, along with 2 cc diluent. This is as the chloride. Succinylcholine iodide was used in almost all earlier experiments, but the fear of administering too large quantities of iodide led all users to switch to the chloride. Succinylcholine chloride is somewhat more potent than the iodide, 100 mg of the chloride equalling 150 mg of the iodide (Richards and Youngman (39)).

Technique of Administration

Mayrhofer (36) does not believe succinylcholine appears to be suitable for use in combination with local analgesics because of the small margin between relaxing dose and the paralyzing dose, and because of the rather painful muscular twitchings (from his personal experience), at the onset of its action.

The particular techniques of administration in relation to the different uses of succinylcholine will largely be covered in the section "CLINICAL INDICATION AND APPLICATIONS", but a discussion of the usual dosages used in single and continuous administrations, and certain precautions, will be given here.

Poulson et al (40) found in their experiments in animals (cats and rabbits) and in volunteer medical students that the degree of muscle-fibrillation depended primarily on the rate of the injection, 20-30 mg succinylcholine in less than 10 seconds invariably giving rise to a 'twitch-reaction' of varying degree. In most cases the same dose administered in the course of 20-30 seconds resulted in less muscle-fibrillations and in about 25% of the cases no twitch was seen by them. When they infused the same dosage (mechanically) in the course of 30-60 seconds, almost no muscle-fibrillation was seen. In most cases the paralysis following rapid injection was complete and of short duration (1-2 minutes). After slow infusion the paralysis was less pronounced, but of longer duration (2-3 minutes). Their experimental results were confirmed by two years of clinical experience with about 2000 administrations of the drug.

Most have abandoned the use of a mixture of barbiturate and all relaxants, since a small proportion of patients complain of suffocation symptoms. Since succi-

nylcholine is also hydrolyzed by the high pH of barbiturate solutions, this is still another reason why they should not be given together. Rose (41) uses the two-syringe method, the succinylcholine following.

Britton and Volpitto (42) found the dosage of succinylcholine in general could be fairly well determined by the age, weight, build and condition of the patient; old, thin, flabby individuals in poor physical condition needed less succinylcholine than healthy persons. In contrast, Durrans (34) believes the response to and the recovery time from, a given dose of a relaxant varies very little with either the age or the physical condition of the patient. He has been very surprised at the tolerance to the drug of the aged and very sick patients, it being his impression that these patients require relatively more relaxant than the fit younger patients, in contrast to experience with thiopentone. Lund (43) finds that the amount varies; the average adult requiring about 30 mg, the robust male requiring about 40 mg, and 10-20 mg sufficing in debilitated, senile adults and in children under 10 years of age. Hurley and Munro (44) find, as a result of experience gained from 156 administrations of succinylcholine as a relaxant in ECT, that 4/5 of the dose is sufficient for women. Price and Rogers (45) originally calculated the dosage in mg of succinylcholine as the

weight in pounds divided by 4. They now use less, however, simply 20-30 mg. Richards and Youngman (39) have found that adequate doses of relaxant drugs always depress respiration to such an extent that it should be assisted or controlled, and if so, they believe there is seldom any point in giving a minimum dose of such a short-acting relaxant as succinylcholine. They usually give a full dose of 100 mg to adults. They do not believe that increasing the dosage makes its effect last any longer. It is evident from Collier's report (20) that in a normal patient the larger the dose of succinylcholine the longer it lasts. Hence it is desirable to use the least dose of the drug possible that will give the needed relaxation. Foldes (46) supports this and believes that the single (1.1 mg/kg) dose advocated in British reports (Bourne (47) and Harper(48)), are unnecessarily high. He has found that in administration to over 400 patients 20-30 mg of succinylcholine was adequate. This was found to give adequate relaxation for 3-5 minutes, long enough for an unhurried intubation, the main use of the single injection. Bourne et al (16) use a 5% solution, and the usual dose expressed in ml. as 1/100 of the body weight in pounds. Thus for a man of 160 pounds the dose was 1.6 ml. (80 mg). For ECT Bourne et al (16) use doses ½ this. They state these doses were safe, but smaller doses were often found

satisfactory. Bourne (49), in replying to Foldes (46), agreed that a dose of succinylcholine less than 1.1 mg/kg is satisfactory for single injection, and states further, "In my experience with 740 patients, using doses within 0.55-1.1 mg/kg, I have occasionally found slight delay in recovery, but in no patient did apnea exceed 15 minutes."

Paton and Zaimis (7) state, "The brevity of action of succinylcholine has led to its use in a novel way, by continuous infusion. This offers the advantage that a very accurate control of depth of relaxation can be obtained, and that when required rapid return to normal can be obtained by stopping the infusion." Foldes (46) has achieved prolonged and readily controllable muscular relaxation by the continuous intravenous administration of dilute succinylcholine solutions. Following the initial dose of 10-30 mg he administered a 0.16% solution at the rate of 10-60 drops/minute (average equals 30), delivering to the patient about 1-5 mg/minute, which seemed to him to be the rate range in which hydrolysis took place. With this method of relaxation, he controlled the intensity of muscular relaxation by changing the rate of the infusion, its effects disappearing completely within 3-5 minutes after stopping its administration. Richards and Youngman (39) use a 0.1% solution, starting the solution immediately after intubation at a rate of about 4 mg/min-

ute (80 drops/minute), which maintains full relaxation, they find. They believe respirations should be assisted or controlled and the rate of infusion should not be varied with respirations as Thesleff et al (14) in Sweden believe. Poulson et al (40) found the paralysis following continuous infusion to be less pronounced but of longer duration than that produced by rapid single injection. Green (50) finds the quantity of drug required for any standard operation to vary considerably from patient to patient and cannot base his dosages upon weight or physique. In 150 operations he gave an average dose by continuous drip of 480 mg/hour; extreme doses were as much as 900 mg/hour and as little as 125 mg/hour, longer operations requiring a slightly lower average hourly dose. He uses a 0.1% solution in normal saline, a test dose first being given slowly by intravenous drip to the conscious patient until some effects are felt, usually a twitching sensation down the spine. He then rapidly follows this rapidly by 0.5 gram thiopentone and increases the drip-rate until good relaxation of the jaw is obtained. The patient is then intubated and anesthetic mixture applied. Respirations are assisted, but at no time completely eliminating spontaneous respirations. The drip-rate is adjusted from time to time to produce the required relaxation for various stages of the operation, i.e., dur-

ing gastrectomy, he finds ~~a finds~~ a fast drip gives good relaxation during abdominal exploration, but during the anastomosis the drip is slowed and some muscle tone allowed to return. Using this procedure he has found muscle tone to return in almost all cases within 5 minutes of stopping the drip. Little et al (17) use a 0.1% solution in glucose in water following induction, until apnea occurs, then intubate. They use the disappearance of muscle-fibrillations as the time to intubate. They increase the drip with opening of the abdomen, and slow it after packs and retractors are in position. The maintenance rate, necessary to provide adequate relaxation without apnea, has been found by them to be approximately 1/3 of the rate which produced apnea. They found maintenance rate to be from 0.7-11.1 mg/min (average equals 4.2 mg/minute), corresponding to 4-12 mg/kg/hour. They have found that this technique has provided continuous relaxation, similar to spinal anesthesia, in operations of over 4 hours duration without evidences of cumulative effect. Morton (51) uses a pendulum of variable length swinging at a given number of times per minute behind the drip chamber, so that the drops are made to keep time with the pendulum. Thesleff et al (14) use 1-2 mg/cc in normal saline at the rate of 40-60 drops/minute, which they state is enough to relax the peripheral muscles but not to paralyze

respirations, 200-400 mg/hour being required. Herington and James (52) use a 0.15% solution in normal saline (750 mg succinylcholine in 500 ml. normal saline).

CLINICAL INDICATIONS AND APPLICATIONS

Little et al (17) state, "The basis for the clinical usefulness of succinylcholine is due to several factors; the rapid hydrolysis into natural metabolites, the extremely brief action of but 2-3 minutes after a full relaxant dose, the controllability of both the degree and the duration of relaxation on a minute to minute basis, and the low toxicity. This has led to its use in the following varied procedures: 1) to facilitate endotracheal intubation, 2) to provide prolonged and continuous muscular relaxation, 3) to provide peritoneal relaxation, 4) to provide adequate relaxation for abdominal closure, 5) to provide adequate sphincter relaxation in hemorrhoidectomy, 6) to provide adequate relaxation for manipulation and reduction of fractures, 7) to provide perineal relaxation during operative vaginal delivery, 8) to provide glottic relaxation to combat severe laryngospasm, 9) to provide adequate relaxation to combat fractures and other complications in electro-shock therapy, and 10) other less

frequent uses, such as tetanus, dental procedures and hiccough."

Intubation
(including bronchoscopy and laryngoscopy)

Mayrhofer (36) found succinylcholine to be particularly useful in facilitating endotracheal intubation, even in patients whom other curarizing agents had failed to produce adequate relaxation. Lund (43) found the vocal cords to be less irritable and adduction of the cords less common than with pentothal. Butt (53) observed excellent relaxation of the vocal cords, permitting easy passage of the bronchoscope with minimal trauma to the larynx. She found laryngospasm was remarkably reduced, and when it did occur, it was very mild. The report of Little et al (17) supports those of Butt (53) and Lund (43), observing that ideal conditions are produced for intubation, and yet, because of its ultra-short action, full muscular activity and spontaneous respirations returned within seconds or minutes. Bourne et al (16) prefer longer-acting relaxants in sub-paralyzing doses for intubation, bronchoscopy and laryngoscopy, as the use of succinylcholine proved difficult for them in these procedures. Hampton et al (54) compared the action of various muscle relaxants in facilitating endotracheal intubation, concluding, "Not only do such muscle relaxants as

d-Tubocurarine, syncurine and flaxedil possess the disadvantage of long activity but they also produce ideal conditions for intubation with less consistency than does succinylcholine."

The dosage for intubation varies, as does the method. Some (Bourne et al (16), Little et al (17) and Thesleff et al (14)), if for long operations, use the infusion technique, the drip varying from 30-60 drops/minute. If intubation is for a short procedure, a single injection, varying from 10 (Foldes (46)) to 100 mg (Richards and Youngman (39)) is used. In most cases the dosage for intubation is used as a test dose (Bourne (49) and Green (50)), to determine the patient's reaction to the drug. Little et al (17) injected initially 10 mg, and after observing its effect in 60 seconds, injected another 10-50 mg (average 30). This was followed by apnea, the patient was hyperventilated with nitrous oxide/oxygen mixture and then intubated. This, in general, is the procedure for intubation, bronchoscopy and laryngoscopy. Foldes (46) and Butt (53) found the relaxation of the cords so profound that no local anesthetic was necessary for laryngoscopy or bronchoscopy.

Laryngospasm

Mayrhofer (36) used succinylcholine several times for laryngospasm and found it quickly and successfully

relieved various degrees of laryngospasm after thiopentone administration. Most (Mayrhofer (36), Foldes (46), Lund (43), Little et al (17) and Butt (53)) feel that the relaxation produced by succinylcholine is so profound, that spraying of the cords is unnecessary, and still the incidence of laryngospasm is markedly reduced. Lund (43) found, in treatment of laryngospasm, that 30-50 mg succinylcholine enabled intubation within 30 seconds, thereby facilitating oxygen therapy.

Abdominal Relaxation

Bourne et al (16) state, "Succinylcholine in abdominal relaxation can be applied in four different ways: a) to supplement curare or gallamine, given both before them for intubation and at the end for sewing up, thereby obviating the need for additional doses of curare or gallamine, making recovery faster, and making the use of their antidote, neostigmine, less often necessary, b) succinylcholine has been used successfully to supplement decamethonium in some old and bronchitic patients, where it was thought inadvisable to give neostigmine, because of its action on bronchial secretion, c) as a sole relaxant and given by frequent repeated injections, and per intravenous drip." Kay (55) states it is the best relaxant for appendectomy. Richards and Youngman (39) believe the time and degree of relaxation for abdominal procedures

is better controlled than with any other relaxant. Typically, for abdominal procedures, an intravenous drip is used. Most use succinylcholine throughout (Mayrhofer (36), Bourne et al (16), Foldes (46), Little et al (17), Lund (43) and Butt (53)), but some use it only in the beginning for intubation and at the end for abdominal closure (Thesleff et al (14), MacKay (56), Lehmann and Silk (22), and Poulson et al (40)). Those who advocate continuous drip increase the rate of the drip when the abdomen is opened and until retractors, etc., are in place, and slow the rate after exploration is completed, especially at the time of anastomosis. The rate is then increased for abdominal closure. Those who advocate succinylcholine at the beginning and at the end of surgical procedures, use the usual dose of 10-50 mg for intubation, and the same amount (if that dose is satisfactory) at the time of peritoneal closure. This way added dosages of longer relaxing agents is not needed at the end, and the recovery of the patient is greatly hastened.

Sphincter Relaxation

Little et al (17) describe the use of succinylcholine for sphincter relaxation in hemorrhoidectomies with the use of repeated doses of 10-20 mg. They found succinylcholine to produce excellent relaxation of the anal

sphincter and obtundation of the potent recto-laryngeal reflex. 10-20 mg were given immediately prior to sphincter dilitation and repeated as necessary for relaxation.

Perineal Relaxation

Little et al (17) and Richards and Youngman (39) have described the use of succinylcholine for perineal relaxation for cephalic version and other difficult obstetrical procedures. Richards and Youngman (39) have used the drug in 12 cases, 100 mg being given after 0.5 gram of thiopentone. When manipulation was prolonged, a second dose was given. Little et al (17) established light general anesthesia, and then gave 10-20 mg immediately prior to the moment of need for perineal relaxation. They found the perineal relaxation so achieved startling in its profundity, thus making it possible to perform difficult operative obstetrics with minimal trauma to the mother. They give a word of caution, however, "In one instance, two 10 mg doses administered within 60 seconds of each other, while providing the desired degree of relaxation, also apparently crossed the placental membrane, for the infant was completely flaccid and apneic upon delivery. Recovery was extremely rapid, spontaneous respirations occuring by the time the cord was cut, but the experience dampened enthusiasm for the utilization of this technique in obstetrics."

This is in direct contrast to the report of Thesleff et al (14), who at the time of caesarian section injected 50 mg succinylcholine into the uterine arteries on three occasions, and reported no adverse effects.

Tetanus

Woolmer and Cates (57) have described a case of tetanus treated successfully with succinylcholine. Bourne et al (16) mention its use. Woolmer and Cates (57) first assessed by single intravenous injections the patient's response to the drug. 10 mg was found to cause complete flaccidity and necessitated artificial respiration with oxygen. Two doses of 2.5 mg two minutes apart were found to cause a decrease in respiratory excursion but without abolishing the trismus. On these findings they gave an intravenous drip of normal saline solution containing 3 mg/ml., the rate being varied to deliver between 1.5 and 3 mg/minute. On this regime they found the patient to be more comfortable and free from major spasms for several hours, but the patient could not swallow or clear her throat. By making minor alterations in the rate of infusion they steered the patient between mild overdosage (diplopia, shallow respiration with cyanosis) and underdosage (painful spasms of the neck and back, together with laryngeal spasms). Their report leaves little doubt that succinylcholine contributed to this patient's recovery.

Larger doses of hypnotic drugs would have been needed to achieve equivalent relaxation, and this would have endangered the already embarassed respiratory system. The change in dosage was thought presumably due to the fact that, as time went on, more toxin was being neutralized by antitoxin, and the acetylcholinesterase balance was moving in the direction of decreased muscle tone. The need to vary dosage and the need to give oxygen with artificial respiration mean that this form of treatment entails virtually continuous medical attention, day and night, for several days. In this case, however, this constant vigilance was rewarded by recovery of the patient.

Electro-shock Therapy

Holmberg and Thesleff (58) state, "Since Bennett in 1940 introduced curare as a prophylactic measure in EST, this method has been widely used. It has not, however, been possible to give sufficiently large doses to prevent fractures entirely. All the preparations hitherto tested have such a prolonged effect that it is necessary to anticipate respiratory failure, necessitating prolonged supervision after therapy." Mayrhofer believes the short-lasting paralysis and the freedom from side-effects make succinylcholine the ideal drug for mitigating the muscle contractions during EST. Price and Rogers (45) found more rapid and more complete modification of the fit than

was possible with gallamine. Thiopentone dosage was found to be less with succinylcholine, making possible a more rapid recovery of the patient, and less fall in the blood pressure. Price and Rogers describe three techniques used: 1) atropine gr 1/75 and thiopentone 250 mg followed by succinylcholine at 20-45 seconds, and oxygen rebreathing for 1 minute after injection of succinylcholine, then application of the current, 2) succinylcholine mixed in the same syringe as atropine and thiopentone and given immediately, inflation with oxygen as before, shock being given at 45-60 seconds, 3) thiopentone 150 mg, atropine 1/75 gr, injected in 4 or 5 seconds, followed by succinylcholine in a 1 ml. syringe at 10 sedonds through the same needle, then inflation with oxygen per mask, shock given at 1 minute. They found that # 3 was the most efficient. Taylor (60) uses 3 gr of Na Amytal 1 hour prior to therapy, and just before shock, 5 mg succinylcholine is given in 10 seconds. Oxygen has been given by him in 50% of his administrations (25 cases). Richards and Youngman (39) use the following proceedure: atropine 1/200 and hyoscine 1/200 gr 3/4 hour before therapy. Thiopentone 0.4-0.6 gram, followed by succinylcholine iodide (50-100) or succinylcholine chloride (30-60) in two minutes. In one minute the shock is applied and the lungs are inflated with oxygen during the

short period of apnea. Thesleff et al (14) give a 150 mg thiopentone and 0.3 mg/kg succinylcholine mixture in 60 seconds, with simultaneous inhalation of oxygen. 20 seconds after termination of the injection, the shock is given. With this technique they found that the majority had only slight muscular twitchings, and the procedure was over in about 7 minutes. Holmberg and Thesleff (58) found that spontaneous respirations occur in 1-2 minutes and when respirations are regular, the patient is returned to the ward safely, in about 5-7 minutes. They use 0.3 mg/kg. The mixture is given slowly for the following reasons: 1) the paralysis does not set in so violently and is not so unpleasant for the patient, 2) the full effect of a barbiturate is not obtained in a shorter time, 3) if the barbiturate is given more rapidly, there is risk of laryngospasm and decrease in blood pressure. When the injection is given, oxygen is given per mask to rule out anoxia during treatment. Equipment for intubation should always be at hand in order to ensure a free airway. This method has been given by them to 136 patients, for a total of 512 therapies. The strength of the contractions were graded as follows: normal, definitely decreased, and slight, the latter meaning the patient was so relaxed that the limbs were not lifted off the bed. In 13 patients the strength of the convulsions was found to be normal

(not definitely decreased), in 57 they were definitely reduced to slight, and in 38 they were slight.

Manipulations

Richards and Youngman (39) use 10-20 mg succinylcholine for manipulations and reductions of fractures, injected slowly to prevent any marked muscle-fibrillations, and found that it gives a more profound relaxation than any other relaxant. Vaz and Bishop (61) first establish light general anesthesia and in 15 seconds inject about 25 mg succinylcholine. They have found that by the time the plaster is applied the patient is recovered sufficiently to need no further attention.

Other Uses

Bourne et al (16), Bourne (49), Vaz and Bishop (61) and Lund (43) have used succinylcholine for prolonged hiccough with good results. Williams (62) has used succinylcholine in 64 dental cases and has found that it gives a more profound relaxation than any other relaxant.

Lund (43) has used succinylcholine to supplement spinal anesthesia since he has found that additional relaxation is frequently needed during the last stages of longer operations.

Bourne et al (16) have used succinylcholine in combination with other relaxants, stating that it does not

interfere with the longer-acting relaxants when used for induction, or when administered at the time of abdominal closure for added relaxation.

SIDE-EFFECTS

Little et al (17) state, "Side-effects as are seen are produced only with large doses, and since succinylcholine resembles acetylcholine in both chemical structure and depolarizing action on the motor end-plate membrane, it is not surprising that the side-effects seen with large doses in some ways mimic the pharmacological effects of acetylcholine. In the dog, for instance, succinylcholine produces salivation, and in the rabbit and guinea-pig, the drug produces some stimulation of the intestine. In large doses that are about 25 times the relaxant dose, succinylcholine has a nicotinic effect upon the blood pressure of experimental animals, causing a hypertension similar to that produced by acetylcholine. This effect was not seen with paralyzant doses in man, however, which have no effect upon blood pressure, heart rate or rythm. Furthermore, succinylcholine does not appear to liberate histamine in man, or at least liberation is less than 1/100 of the amount produced by d-Tubocurarine. Finally, succinylcholine does not appear to block

autonomic ganglia in either man or experimental animals." Britton and Volpitto (42) found no unwanted side-effects except for muscular twitchings accompanied by increase in depth of respirations when succinylcholine was injected too rapidly. Bovet et al (10) and Brucke et al (15) found that succinylcholine causes an increase in flow of saliva. Bourne et al (16) have been unable to confirm this experimentally in man, finding that no increase in flow of saliva occurred in patients who received premedication with papaveretum and in those who received none.

Gray (63) noticed after giving the following sequence of drugs - d-Tubocurarine, succinylcholine, atropine, neostigmine and succinylcholine - the last dose of the latter being 25 mg, a most alarming bradycardia (30) followed by vomiting of what appeared to be recently secreted stomach contents. He thought it was inconceivably related to the succinylcholine but gave a possible mechanism of intense inhibition of tissue cholinesterase due to the combined action of neostigmine and succinylcholine.

Green (50), in his observations with the use of succinylcholine, has noticed an increased blood pressure in 25% of the cases, and a decreased pulse rate in 40% of the cases.

Franks (64) has found one apparent drawback to the use of the drug, i.e., a tendency to increased bleeding

associated with a moderate hypertensive effect.

Foldes et al (27) found no harmful side-effects in the dose-range of succinylcholine employed.

Prolonged Apnea

Bourne et al (16) reported apnea lasting between 8 and 15 minutes in 5 of 546 patients. Evans et al (24) found only 2 long-reactors in more than 400 patients. Richards and Youngman (39) noted no long reactions in 250 patients, and Foldes (46) saw none in 400. Butt (53) noted apnea exceeding 6 minutes in only one patient in 1,000. Herington and James (52) noted no prolonged apnea in 289 cases. Of an aggregate therefore of almost 3000 reported cases, apnea exceeded 7 minutes in only 8, and 21 minutes in none. Collier (20) states, "Several possibilities, which have not always been excluded, should be considered in examining the cause of prolonged action after the use of succinylcholine. It is possible that manual ventilation helps to prolong apnea through 1) acapnea, 2) the Hering-Breuer reflex, and 3) potentiation of other drugs used in anesthesia, such as thiopentone." Durrans (34) has discussed the associated possibility that drugs other than succinylcholine may cause prolonged apnea and gives reasons suggesting that the effect is due to depression of the respiratory centre. Barron (65) terminated some prolonged apneas after succinylcholine with niketha-

mide, supporting this view, since nikethamide is well known to antagonize central respiratory depressants.

The importance of the 'pseudo'-cholinesterase level has been brought out by Bourne et al (16), Evans et al (24), MacKay (56), Harper (48) and Grant (67) and Evans et al (66). Evans et al (66), stimulated by studies of Whittaker and Wijesundera (23) on serum-esterase levels of human plasma, determined the levels of 'pseudo'-cholinesterase in 2 patients who had reacted to standard doses of succinylcholine with paralyses of 20 and 21 minutes. They found the levels to be very low, both being 12 units, and the levels of 4 patients who responded normally to be from 55-98 units. Bourne et al (16) studied the 'pseudo'-cholinesterase levels of 6 normally reacting patients and 6 who had reacted to standard doses with apnea over 8 minutes. They found the levels in the normally reacting patients, in Callaway (33) units, to be 88.5 ± 6.9, and in the long reactors to be 38.3 ± 6.8 units.

Treatment of Prolonged Apnea

The following suggestions have been made as to how to deal with long reaction : 1) reduction of the doses of drugs liable to depress the respiratory centre and avoidance of hyperventilation. Durrans (34), Barron (65) and Richards and Youngman (39) give evidence that implicates central respiratory depression as the cause of the

prolonged apneas seen after succinylcholine. It is therefore logical to reduce the doses of drugs such as papaveretum and thiopentone. 2) Reduction to a minimum of the dose of succinylcholine used. Foldes (46) and Lehmann and Silk (22) give evidence that the larger the dose the longer the action, hence it is desirable to use the least dose of succinylcholine possible that will give the needed relaxation. In contrast, Wolfers (68) believes that a patient's response to succinylcholine varies from day to day, and it is hard for him to accept the theory of overdosage or depressants causing prolonged response. 3) Observation of special caution in patients likely to have a low plasma-cholinesterase, e.g., those suffering from starvation, liver disease, anemia, and exposure to certain insecticides. Bourne et al (16), Bourne (49), Grant (67), Harper (48), Cowan (69), Harrison et al (70) and MacKay (56) stress the importance of this observation in preventing prolonged action. Cowan (69) cites a case of severe gastrointestinal bleeding which had to be transfused with 7 pints of blood. At the end of gastric surgery, succinylcholine was given and complete apnea resulted. Respirations did not return until a pint of 2 hour old blood had been given. The plasma-cholinesterase was found to be 8 units. Harrison et al (70) report similar results after 1/3 of a pint of fresh blood had been given.

Harper (48) and Thesleff (32) suggest the possibility of a cholinesterase inhibitor, e.g., T.E.E.P. Callaway et al (33) have shown, however, that workers in insecticide factories have only slightly, to no, depression of their plasma-cholinesterase levels. They also found that in the average adult population, low plasma-cholinesterase levels are extremely rare. Grant (67) suggests routine plasma-cholinesterase measurements, but this determination at present is impracticable. 4) Preliminary test dose of succinylcholine. When it is intended to give repeated doses or continuous intravenous drip, the first dose (for intubation) can be regarded as the test dose. This procedure was first suggested and tried by Bourne et al (16). 5) A preliminary test dose of acetylcholine. Collier (20) states this would be of little value because the acetylcholine would be destroyed by the cell, or 'true'-cholinesterase. 6) Use of an antagonist. Theoretically the obvious antagonist is 'pseudo'-cholinesterase itself; and Evans et al (66), Cowan (69), Harrison et al (70), Bourne (49) and Barnard (71) reported its effectiveness in a few cases. As Lehmann and Silk (22) and Bourne et al (16) point out, fresh plasma or whole blood might be used, but it would require a large transfusion to appreciably raise the enzyme concentration of the recipient's plasma. This has been borne out by experiences of Harrison et al (70) and Barnard (71), who had cases of pro-

longed response refractive to transfusion of day-old blood, but, after the administration of blood only a few hours old, the patients recovered quite promptly.

ADVANTAGES

Foldes et al (27) state, " The specificity and rapid onset of action of succinylcholine, its readily controllability, its wide margin between muscular relaxation and respiratory arrest and rapid and complete recovery after the cessation of its administration establish it as unsurpassed in the field of muscular relaxants. There has been no evidence of unwanted side-effects such as increased salivation, bronchospasm, tachycardia, hypotension or hypertension. No other agent in anesthesia can be as readily controlled as succinylcholine. It has a relative sparing action on respiration. Movements are smooth and less diminished than produced by other relaxants. No evidences of blocking or stimulating the autonomic ganglia have been noted in man. There is less depressant action of the CNS (as evidenced by the fact that the per minute dose of pentothal is greater with succinylcholine than with other relaxants)." Ellis et al (38) have shown experimentally that succinylcholine has less central respiratory depression action. Britton and Volpitto (21) found it to

produce ideal conditions for transition to inhalation anesthesia. Swerdlow (72) emphasized the advantages of succinylcholine due to its short action, and thus rapid return of muscle tone, giving support to the veins and thus aiding venous return and cardiac output. Its short action also facilitates rapid return of the cough reflex, decreasing the incidence of post-operative chest complications. Lund (43), Bourne et al (16) and Thesleff (32) emphasize the fact that succinylcholine is metabolized into normal metabolic or natural products.

DISADVANTAGES

Foldes et al (27) state, " The disadvantages are not serious: 1) the administrations require greater attention on the part of the anesthesiologist. 2) Somewhat higher doses of pentothal were required with succinylcholine than with other relaxants. Consequently, the average recovery time of patients who had been given succinylcholine and pentothal was considerably longer than when other relaxants were used (79 as compared to 33-58 minutes)."

Little et al (17) report a case of flaccidity in a newborn when succinylcholine was used for perineal relaxation, thus it apparently crosses the placental barrier. Swerdlow (72) thought some patients were unable to keep

pace with the rate of succinylcholine administration.

Williams (62) thought there seemed to be more hemorrhage with the use of succinylcholine.

SUMMARY

1. Succinylcholine was first mentioned in 1921, but it was not until 1949 that its potent neuromuscular blocking activity was discovered, because the original experiments were on curarized animals. It was first hydrolyzed in 1941. It was not until 1951 and 1952 that succinylcholine was found suitable for clinical use.
2. Succinylcholine closely resembles acetylcholine, having a depolarizing action probably like that of acetylcholine in that it acts on the end-plate.
3. The drug acts ½-1 minute after intravenous injection and the effects are usually dissipated within 2-4 minutes. Paralysis begins in the muscles of the eye, as evidenced by diplopia, and progresses to the pharynx, thence to muscles of the body, except the diaphragm, which is last effected. Thus the order of paralysis is the same as with the other relaxants. Fine muscle-fibrillations are seen 12-15 seconds after the injection, thought to be a manifestation of depolarization of the end-plate. Their termination signifies the onset of paralysis. The speed

of action of succinylcholine depends upon the speed of its removal by 'pseudo'-cholinesterase of the plasma, therefore it might be wise not to give succinylcholine to patients likely to have a low serum-esterase level; such may be found in anemia, inanition and possibly those suffering from insecticide poisoning. Low 'pseudo'-cholinesterase levels have been demonstrated in several patients who reacted abnormally long to the drug.

4. In comparison with other relaxants, succinylcholine was found to have the strongest neuromuscular blocking effect and the weakest stimulating effect to the autonomic ganglia. Since its action is due to end-plate depolarization, it is not counteracted by anti-cholinesterases, such as neostigmine, as is d-Tubocurarine and flaxedil. Its action is prolonged by such drugs. Succinylcholine resembles decamethonium in action, but differs from that drug in being hydrolyzed by serum-esterases. Compared with d-Tubocurarine, succinylcholine produces little or no histamine liberation. The latter is about 3 times as potent and has a histamine-liberating effect about 1/100 as great as that of d-Tubocurarine. Due to its potency it has a relative sparing action on respiration.

5. Toxicity studies have revealed that animals could withstand enormous doses of succinylcholine without any deleterious effects.

6. Succinylcholine ('Anectine', Burroughs Wellcome; 'Quellicin', Abbott; 'Sucostrin', Squibb) is supplied in 10 cc multiple dose vials, 20 mg/cc; 10 cc ampuls, 50 mg/cc; and ampuls of 100 mg. dry substance. The drug is supplied as the chloride. The iodide is not used as extensively as the chloride because of the fear of administering too great quantities of iodine.

7. Succinylcholine should be used only by anestheliogists with anesthetic equipment.

8. Succinylcholine should be given slowly (about 30 seconds) to prevent muscle-fibrillations. It should not be mixed with barbiturate solutions unless given immediately as the alkaline pH of these solutions rapidly hydrolyzes succinylcholine.

9. The dosage used varies greatly, according to the administrator, but generally it is accepted that the smallest dose that will produce adequate relaxation should be given. This is usually in the range of 10-50 mg for single injections, and between 30 and 60 drops/minute of a 0.1% solution for intravenous infusion. Averages are: 30 mg. for single injection and 30 drops/minute for intravenous infusion. 100 mg. of the chloride is equivalent to 150 mg. of the iodide.

10. Rapid hydrolysis into normal metabolites, extremely brief action of but 2-3 minutes, the controllability

of both the degree and the duration of relaxation on a minute to minute basis, and the low toxicity, form the basis for succinylcholine's wide clinical usefulness. This has led to its use in facilitating endotracheal intubation, providing prolonged and continuous muscular relaxation, obtaining peritoneal relaxation, relaxation for abdominal closure, sphincter relaxation, relaxation for manipulations and reductions, perineal relaxation during operative vaginal delivery, glottic relaxation for laryngospasm, relaxation during electro-shock therapy, and other less frequent uses such as tetanus, dental procedures and hiccough. It has been found that succinylcholine produces ideal conditions for all the above usages with greater consistency than any of the other relaxants.

11. The side-effects seen with succinylcholine are minor and few. It has no effect on the heart, blood pressure, CNS, salivation or histamine liberation (as evidenced by absence of bronchospasm or laryngospasm and absence of wheel on skin testing). There are conflicting reports about the effect of succinylcholine upon the gut, both experimentally and clinically, although most users of the drug in abdominal procedures slow up the infusion when gut anastomoses are being made. This might suggest that succinylcholine stimulates, or has a cholinergic action, upon the gut. There has been only one report of brady-

cardia and vomiting following administration of succinylcholine, and the evidence would seem to point more to the neostigmine which was also administered. In one report of 50 cases, an increased blood pressure in 25% and a slowed pulse rate in 40% was noted. There has been one report of the observation of apparent increased bleeding with the use of succinylcholine, although there has been no confirmation or support of this observation by other authors.

12. Apnea is considered as the main side-effect of succinylcholine, yet there have been reports of only 8 cases of prolonged apnea (more than eight minutes) in almost 3000 cases of its use. An investigation of the causes seems to lead to a deficiency of 'pseudo'-cholinesterase of the plasma. This has been confirmed by several authors by the determination of the serum-levels of those patients who reacted abnormally to the drug, with the finding of low 'pseudo'-cholinesterase levels.

13. The advantages of succinylcholine stem from its brevity of action, hydrolysis into natural metabolites of succinic acid and choline, absence of side-effects and readily controllability. It is not contraindicated in those patients afflicted with myasthenia gravis.

14. The disadvantages arise mainly from the constant attention required when administering the drug, therefore

having nothing to do with the patient as far as adverse effects. A further disadvantage, although it is rarely encountered, is the occasional long-reactor to the drug. These patients are also poor surgical risks, however, those who have severe anemia, suffer from severe malnutrition, post-irradiation patients, and possibly patients suffering from insecticide poisoning.

CONCLUSION

The results of clinical administration of succinylcholine seem to have justified extreme degrees of enthusiasm because of its potent ability to paralyze, and, in addition, it resembles acetylcholine, so that it is rapidly hydrolyzed into natural metabolites which apparently have no deleterious effects upon the human body. The duration of its action is much less than other relaxants giving it a great range of controllability. A word of caution could well be mentioned, however, because of its potency. This means that only those who are familiar with its actions and familiar with all types of anesthesia, should be permitted to use this drug. The infusion technique is fraught with dangers - it demands the absolute and undivided attention of the anesthesiologist at all times; furthermore, even the extensive trials both in the United

States and in Europe have failed to provide conclusive evidence to answer some vital questions: the effects upon the liver, upon the kidney, upon the CNS, and upon the cardiovascular system, including the bleeding mechanisms, both under normal conditions as well as in the presence of all manner of pathological processes.

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