UNTOWARD REACTIONS TO SUCCINYLCHOLINE*

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THE INTRODUCTION of curare into clinical anaesthesia by Griffith (1) in 1942 was undoubtedly a major advance in anaesthesia, aptly described by Gray as a "flash of inspired genius" (2). Little and co-authors (3) have pointed out that the sheer brilliance of Griffith's contribution has dominated the trend in the specialty of anaesthesiology for over a decade. Whatever one's opinion may be regarding the toxic potentialities of curare, the basic concept of producing muscular relaxation by a drug acting directly at the neuromuscular junction, rather than by the profound depression of general anaesthesia, is firmly established, and one must agree with an opinion expressed by Griffith in 1954, that muscle relaxants are here to stay (4).

With the general acceptance of such a revolutionary principle, it was to be expected that an intensive search would be made for the ideal muscle relaxant. Numerous drugs have been introduced and given extensive clinical trial, and of these, succinylcholine seems to come closest to the ideal requirements (5, 6). Many excellent and often enthusiastic reports on the many uses of succinylcholine have been published and reference is made to only a few of these (7-19).

Most therapeutic agents and methods, when their effectiveness has been firmly established, pass through a period of over-use, misuse and over-enthusiasm, to be followed by a phase of reaction, disappointment, and often unjustified condemnation. The purpose of this paper is to attempt to evaluate the disadvantages and untoward reactions to succinylcholine, which is an agent of proved value.

Succinylcholine is known by a wide variety of trade names and chemically also as succinyldicholine, diacetylcholine, and suxamethonium. Further confusion is added when comparing dosages of the different salts. In this paper, doses, when mentioned, will be expressed in terms of the active cation and the drug will be referred to as succinylcholine, as this name is in general use in North America.

MISUSE

If misused, any potent agent will produce undesirable effects. Like any muscle relaxant, succinylcholine will produce varying degrees of respiratory depression, and it has been emphasized repeatedly that, with all such agents, respiration must be controlled or assisted at all times if the vicious effects of anoxia and carbon dioxide retention are to be avoided.

APPARENT LACK OF POTENCY

If administration of succinylcholine does not produce the anticipated effects, it is advisable to make sure that the drug has actually been given intravenously.

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However, loss of potency may occur during storage of solutions. When succinylcholine chloride is stored at 75°C, the drug is 92 per cent potent in three months and 81 per cent at the end of six months (20). As the products of hydrolysis are, progressively, succinylmonocholine, succinic acid, and choline (as *in vivo*) no harm would be expected from giving a deteriorated solution, unless large amounts of succinylmonocholine were given. The pharmacology of succinylmonocholine is of importance in all considerations of the reactions to succinylcholine. Briefly, succinylmonocholine has actions similar to those of succinylcholine, but in the human about 1/40th to 1/50th of its activity, and is hydrolysed much more slowly by pseudo-cholinesterase under clinical conditions (21, 22).

On five separate occasions when using a solution of succinylcholine chloride by continuous intravenous drip, I did not obtain the effect one would expect, and when a change was made to an intravenous drip of a freshly prepared solution of succinylcholine bromide powder the anticipated effect was obtained in all cases.

Resistance of patients suffering from myasthenia gravis to succinylcholine has been described (23, 24). Succinylcholine was given to five patients suffering from myasthenia gravis. In four patients receiving regular maintenance doses of prostigmine, 60 mgm. of succinylcholine produced an expected and normal response. The fifth patient, who had not received any prostigmine, was not relaxed at all with 60 mgm. of succinylcholine, and a further dose of 60 mgm., given within one minute, produced only a very slight effect of muscular relaxation.

MUSCLE TWITCHINGS OR FASCICULATIONS

Though frequently seen, muscle fasciculations cause few reported complications. Postoperative muscle soreness lasting for a few days sometimes occurs. The muscle fasciculations were originally attributed by Foldes (25) to the initial stimulating effect of a depolarizing compound on skeletal muscle, but Paton (26) has suggested that the fascicular twitching is due to centripetal antidromic impulses in the motor nerve axon, which bring about a synchronous discharge of the whole motor unit. Churchill-Davidson (27) found that when the injection of succinylcholine was preceded by 40 mgm. of Flaxedil, visible muscle twitching was invariably abolished and the incidence and severity of muscle pains were diminished but not abolished. It has been reported that muscle fasciculations are stronger when the level of plasma pseudo-cholinesterase is high. The severity of muscle twitching and after pains seems to be related to the rate of injection and depth of general anaesthesia, and for this reason it has been suggested that succinylcholine is unsuitable for use as a muscle relaxant for outpatient procedures. In the cases in which I have used succinylcholine, severe muscle stiffness was noted in seven patients all of whom had been anaesthetized for minor procedures, and this gives an incidence of roughly 1.2 per cent. Unfortunate displacement of fracture ends has resulted from violent muscle spasm preceding manipulation.

EFFECTS ON THE AUTONOMIC NERVOUS SYSTEM

These have been carefully looked for, and as succinylcholine is closely related chemically to acetylcholine, it is not surprising that both muscarine and nicotine-like effects may be produced.

Salivation is often noted and is sometimes profuse, particularly during light anaesthesia and in patients who have not received adequate dosage of atropine (or other drying agents). Hypersecretion of bronchial glands does not appear to occur.

Laryngeal and bronchial spasm, though they may occur, are not directly attributable to succinylcholine and are caused by errors in technique, such as failure to complete intubation before the relaxing effects have worn off, or by the irritating effects of an endotracheal tube (particularly if the cuff is inflated), if the patient is inadequately anaesthetized.

EFFECTS ON THE CARDIOVASCULAR SYSTEM

Some observers have reported few significant clinical effects of succinylcholine on the cardiovascular system. However, on closer investigation many effects have been recorded. Cardiac irregularities on endotracheal intubation with various combinations of agents have been described, so it is not surprising that similar reactions occur when succinylcholine has been used to facilitate intubation.

Somers (28), investigating the effects of succinylcholine on the cardiovascular system of cats and dogs, found an obvious nicotinic effect in most animals, but no evidence of a muscarine effect. Clinically the commonest reactions are elevated blood pressure, cardiac irregularities and bradycardia, followed by tachycardia in about 40 per cent of one series of cases (29). Bourne has described an increase in the height of the T-wave from 2 to 4 mm (30), and Phillips (31) found various changes following endotracheal intubation, including cardiac irregularities as shown on the electrocardiographic tracing, such as auricular standstill, nodal rhythm, and ventricular extra systoles. However, the number of cases in which succinylcholine was given before and after pentothal anaesthesia were not reported, nor was the incidence of the observed untoward effects, though it was pointed out that most of the physiological changes could be avoided if succinylcholine were administered following intravenous barbiturate anaesthesia.

Johnstone (32), investigating the effects of succinylcholine on the cardiovascular system of 100 patients who had been premedicated with atropine and anaesthetized with small doses of pentothal, found slight slowing of the pulse in 28 cases, and definite bradycardia in 32 cases with pacemaker shift to the A-V node in 7 patients. This bradycardia was usually followed in about two minutes by a brisk tachycardia. These muscarine effects could be modified by atropine, but not always prevented in the dosage prescribed. In 30 per cent of his cases, flattening of the T-wave with depression of the S T segment was seen. This was not influenced by atropine, and was unrelated to heart rate. He described four instances of severe cardiovascular collapse following administration of succinylcholine to fit young men. These changes are similar to those caused by acetylcholine. However, in spite of all these effects, Johnstone concluded that succinylcholine provides better and safer conditions for endotracheal intubation than other relaxants.

Regarding blood pressure changes, one often sees a slight transient hypertension after a single dose, and prolonged mild hypertension after continuous

drip infusion of succinylcholine. The initial hypertension has been attributed to an asphyxial type of response in the absence of adequate ventilation, possibly aggravated by the muscular activity. The prolonged pressor response is attributed by Paton (33) to the nicotinic effects of succinylcholine and succinylmonocholine and these are not influenced by atropine.

Griffith (34) has emphasized that insidious carbon dioxide accumulation cannot always be excluded as a contributing factor to these late rises in blood pressure.

Little (35) found an infusion of succinylcholine a very useful agent in the anaesthetic technique for mitral commissurotomy and found no deleterious effects on the cardiovascular system in these seriously ill patients.

RELEASE OF HISTAMINE

In large doses succinylcholine can cause histamine release, but is about 100 times less liable to do so than d-tubocurarine. As much larger doses of succinylcholine may be given, even a comparatively slight activity of this sort may be of significance (36), though this does not seem to be of practical importance.

INSUFFICIENT ANAESTHESIA

Cases of patients regaining consciousness while paralysed with curare have been recorded (37); this unpleasant complication has occurred in one of my cases, and I have heard first hand of two others (38).

SUCCINYLCHOLINE IN OBSTETRICS

Succinylcholine has been shown by Pittinger and co-workers (39) to be capable of crossing the placental barrier if the concentration in the uterine artery is sufficiently high. Stead (40), using succinylcholine in 300 neonates, found no prolonged response in spite of the infants' low normal pseudo-cholinesterase level. Succinylcholine has been used by many anaesthetists in combination with general anaesthesia during Caesarian section, and also to produce perineal relaxation during vaginal delivery (41), but no case of respiratory depression of the babies has been attributed to the use of succinylcholine.

RESPIRATORY SYSTEM

As with all muscle relaxants, when succinylcholine produces muscular relaxation there is depression of respiratory activity, and the "relative sparing effect on respiration" reported by Foldes (42) in 1952 has not been confirmed. However, as the degree of relaxation is controllable when a continuous drip is used, it is often possible to produce relaxation adequate for surgical procedures, with minimal respiratory depression.

The most important clinical untoward effect with succinylcholine has been prolonged apnoea, and this complication has been reported at least fifty times, including some interesting cases (43-54). The incidence of prolonged apnoea is given by Bourne (55) as 15 out of 1000 patients. Of these, ten had a pseudo-cholinesterase level below normal or low normal.

Using succinylcholine in over 600 cases, I have encountered three patients who were unusually sensitive to the drug. In one patient suffering from ulcerative colitis, 60 mgm. of succinylcholine produced apnoea for 10 minutes, and abdominal relaxation was adequate for 1½ hours with a further 100 mgm. by intermittent intravenous drip. A patient suffering from abdominal obstruction was apnoeic for 35 minutes after 60 mgm. of succinylcholine and this period of profound relaxation was long enough for the operation to be completed.

Succinylcholine (in 60 mgm. dosage) was given to 87 patients with known clinical liver damage, and of these one patient was unduly sensitive to succinylcholine. A dose of 60 mgm. produced apnoea for 29 minutes, the return of muscle tone and respiratory activity being quite sudden. Subsequent intermittent doses of succinylcholine were given to provide muscular relaxation for the operation (cholecystectomy) and produced apnoea for the following times:

20 mgm.	10 min.
20 mgm.	13 min.
10 mgm	9 min
10 mgm	16 min.
5 mgm.	20 min
2 mgm	10 min.
2 mgm.	21 min

Near completion of the operation, one bottle of stored blood (four days old) was given and after this 2 mgm of succinylcholine produced apnoea for 6 minutes. From these figures it would seem that although cumulative effects of succinylcholine are not seen in normal patients (56), increasing sensitivity may be present in patients who show an abnormal response. This patient was a farmer's wife, but denied contact with organic phosphorous insecticides. Unfortunately it was not possible to estimate her pseudo-cholinesterase level at that time.

The cause of prolonged apnoea is not always clear, as many different factors may be involved. At one time prolonged apnoea was attributed by Foldes (57) simply to over-dosage, but other factors include: (1) the associated respiratory depressant drugs used, (2) apnoea from hyperventilation; (3) distension of the lungs interfering with the Hering-Breuer reflex; (4) a direct depressing effect of succinylcholine on the respiratory centre (58); (5) hypo-calcaemia associated with muscular spasms (59); (6) temporary interference with the electrolyte balance, particularly potassium imbalance; (7) the muscle relaxing effects of succinylmonocholine produced by incomplete hydrolysis; (8) carbon dioxide retention and anoxia. The latter is probably an important factor, as in many reported cases recovery of consciousness was delayed beyond expectation.

However, it seems clear from the work of Evans and co-workers (60), that the usual cause of prolonged apnoea is a lowered plasma pseudo-cholinesterase level, and a definite correlation has been shown to exist between the pseudo-cholinesterase level and the duration of apnoea following succinylcholine.

Pseudo-cholinesterase levels have been investigated in health and disease (61) and low levels have been shown to be sometimes present in cases of liver disease, cachexia, and anaemia and in the severe malnutrition of Kwashiorkor (62). A delayed recovery may be seen in cases of intestinal obstruction, and an increased

response to succinylcholine has been shown to occur in rats following experimental intestinal trauma (63).

Low levels of cholinesterases can be expected in patients after administration of anti-cholinesterases such as prostigmine and Tensilon, and exposure to alkyl pyrophosphates (such as D.F.P.) used in agriculture as insecticides. As pseudo-cholinesterase hydrolyses other esters, the simultaneous administration of succinylcholine and a local anaesthetic agent containing an ester linkage can be expected to cause a prolonged effect of succinylcholine, and this has been confirmed (64).

Low pseudo-cholinesterase levels can occur in patients healthy in other respects (65) and Forbat (66) has described a family of Cypriots with an unexplained low pseudo-cholinesterase level, presumably a genetic inheritance. Callaway (67) has stated that the incidence of patients with low pseudo-cholinesterase level must be extremely rare in healthy subjects. However, the estimation may be desirable under some circumstances. At least four different methods of estimation have been described, each of which expresses the results by a different means. The commonest method seems to be the Warburg manometric method of McArdle (68); by it normal figures are said to be 80-130 units per cc. of plasma. To avoid confusion, Hink (69) has suggested that clinical units be adopted, 1 clinical unit being defined as the cholinesterase activity of 1 cc. of fresh normal pooled plasma. Thus, fresh plasma would contain about 1000 clinical units per litre. As 20 clinical units will quickly reverse the effects of 1 mgm. of succinylcholine, 1 litre of fresh plasma would be expected to neutralize 50 mgm. of succinylcholine and a healthy normal adult could be expected to deal with 300 mgm. of succinylcholine fairly quickly. On storing blood or plasma the value decreases, and stored blood could be expected to contain at least 300 clinical units per litre (70).

Pseudo-cholinesterase has been purified by Cutter Laboratories and named Cholase, and is a subfraction of Cohn's globulin fraction IV-6. Both blood (71) and Cholase (72) have proved effective in shortening the duration of apnoea, but at present Cholase is available only for clinical investigation. As 1 cc. of Cholase has a cholinesterase activity of 350 clinical units, 4-8 cc is the recommended dose in the treatment of prolonged apnoea (73).

Some puzzling cases still remain, such as one in which a normal response was obtained after two or more injections of succinylcholine, and a final dose produced prolonged apnoea (74), in other cases a final dose of succinylcholine produced prolonged apnoea, when normal respiration had returned after using succinylcholine and other muscle relaxants (75-76); prolonged apnoea occurred after using succinylcholine in a case of myasthenia gravis, where one would expect the patient to be resistant to the effects of de-polarizing agents (77). In all these cases, the pseudo-cholinesterase level was normal and the prolonged apnoea responded to anti-cholinesterases. The probable explanation is that succinylcholine produces what Paton describes as "a dual mode of response to de-polarising agents" (78). A similar explanation has been given by Hunter (79). Apart from Cholase and plasma, pharmacological antidotes are at present of little practical value, and it seems that spontaneous respiratory activity will eventually return if the patient is kept alive long enough by artificial respiration.

The longest recorded period is respiratory paralysis lasting into the third day (80) and even shorter periods must be, for the anaesthetist, a tiring and embarrassing time.

Although prolonged apnoea is rare, it is not unusual to encounter prolonged partial respiratory depression after even moderate doses of succinylcholine. This is evidenced by decreased tidal volume, tracheal tug, and probably slight cyanosis. The patients, if awake, will complain of dyspnoea. Accumulation of succinylmonocholine may be a contributing factor, but the usual cause is carbon dioxide retention with or without oxygen lack, caused by inadequate ventilation. This view is supported by the large amounts of succinylcholine which can be given without untoward effects (22.5 gm. has been given over five and a half days in the treatment of tetanus (81)); by the report by Scurr (82) of carbon dioxide retention simulating curarization; by the fact that large doses of Chlase do not reverse these particular effects (83) and that, experimentally, if dogs are ventilated with 20 per cent carbon dioxide, prolongation of muscular insufficiency caused by succinylcholine occurs (84).

The treatment is to eliminate the carbon dioxide by mechanically increasing the tidal volume, for if oxygen alone is given the improvement in colour may be deceptively dangerous.

SUMMARY AND CONCLUSIONS

The untoward effects of succinylcholine have been briefly reviewed.

The seriousness, significance, and manner of causation of these effects have been superficially discussed in the light of present knowledge.

It is concluded that the untoward effects directly attributable to the drug are either of little significance or of rare occurrence. Some are of more theoretical and pharmacological than practical interest, and most can be avoided or minimized by careful use of the drug and well-ménaged anaesthesia.

RÉSUMÉ

L'introduction par Griffith du curare en anesthésie a établi un concept de production de relâchement musculaire par emploi de curarisants plutôt que par dépression profonde par anesthésie générale comme on procédait depuis nombre d'années. Il s'en suivit des recherches extensives pour trouver le curarisant idéal. De tous les médicaments qui ont subi l'épreuve clinique la succinylcholine semble approcher de plus près l'idéal.

Comme les autres curarisants, la succinylcholine produit une dépression respiratoire de degré variable et l'on doit contrôler ou assister la respiration si l'on veut éviter les effets nocifs de l'anoxie et de la rétention du dioxyde de carbone.

Si une solution de succinylcholine ne produit pas l'effet anticipé cela peut être dû à l'injection en dehors de la veine, à la détérioration de la solution, ou encore, la résistance aux effets du médicament chez les patients souffrant de myasthénie grave.

Des contractions ou fibrillations musculaires suivent l'injection de succinyl-

choline et leur sévérité dépend de la vitesse d'injection et du degré d'anesthésie générale. Elles causent peu de complications mais quand elles sont sévères elles peuvent occasionner des douleurs musculaires pour quelques jours. A l'occasion, un déplacement malencontreux de fracture peut se produire à la suite de violents spasmes musculaires de ce genre.

La succinylcholine peut produire des effets ressemblants à ceux de la muscarine et de la nicotine sur le système nerveux autonome. Parfois il y a salivation profuse qui ne semble pas s'accompagner d'hypersécrétion des glandes bronchiques.

On a aussi noté quelques uns des effets de la succinylcholine sur le système cardio-vasculaire. On a rapporté des élévations de pression artérielle, des irrégularités cardiaques, de la bradycardie et de la tachycardie. On a décrit quatre cas de collapse cardio-vasculaire chez de jeunes hommes en bonne condition, suivant l'administration de succinylcholine.

La réaction la plus nuisible que peut suivre l'emploi de la succinylcholine est une apnée prolongée. La plupart des patients qui en souffrent ont une pauvre concentration plasmatique active de pseudo-cholinestérase. Cependant, chez certains, la cause est inconnue. Comme autres facteurs on peut inclure: (1) l'usage d'autres dépressifs respiratoires, (2) l'apnée due à l'hyperventilation; (3) la distension pulmonaire perturbant le reflexe d'Hering-Breuer; (4) un effet dépressif direct de la succinylcholine sur le centre respiratoire; (5) l'hypocalcémie qui accompagne les spasmes musculaires; (6) les modifications temporaires de l'équilibre électrolytique, particulièrement le déséquilibre du potassium, (7) les effets de relâchement musculaire de la succinylcholine produits par hydrolyse incomplète; (8) la retention du dioxyde de carbone et l'anoxie. L'apnée prolongée, dans certains cas, peut être due à la "double réaction" décrite par Paton.

On peut conclure en disant que les effets nuisibles qui peuvent être attribuer directement au médicament sont de peu d'importance ou se produisent rarement. La plupart peuvent être évités ou diminués en employant le médicament prudemment et en donnant une bonne anesthésie.

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