PROLONGED APNOEA FOLLOWING E.C.T. MODIFIED BY SUXETHONIUM (BREVIDIL "E")

By

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THERE have been numerous reports in recent years of prolonged apnoea resulting from the use of suxamethonium (succinylcholine, "Scoline") in general anaesthesia and for electroplexy. For example, Grant (16) described a case of respiratory paralysis lasting 2 to 3 post-operative days following an intravenous dose of 80 mg. of suxamethonium, and Cowan (7) reported a patient who underwent a partial gastrectomy and exhibited complete apnoea for 9 hours duration after only 25 mg. of suxamethonium had been given, and who subsequently died. Hurley and Monro (22) reported apnoea lasting for 10 minutes following 20 mg. of suxamethonium used as a relaxant for electroplexy, and for 20 minutes after decamethonium iodide.

Respiratory paralysis of a duration comparable to that recorded after suxamethonium, does not so far appear to have been described in association with suxethonium (Brevidil "E"), the di-ethyl derivative of suxamethonium, which is surprising in view of the close structural similarity between these two relaxants as indicated by their chemical formulae.

$$\begin{array}{l} CH_2\text{-}COOCH_2\text{-}CH_2\text{-}N\text{-}(CH_3)_2\text{-}C_2H_5Br \\ | \\ CH_2\text{-}COOCH_2\text{-}CH_2\text{-}N\text{-}(CH_3)_2\text{-}C_2H_5Br \end{array}$$

Suxethonium Bromide (Brevidil "E")

$$\begin{array}{l} CH_2\text{-}COOCH_2\text{-}CH_2N\text{-}(CH_3)_3\text{-}Cl \\ | \\ CH_2\text{-}COOCH_2\text{-}CH_2N(CH_3)_3\text{-}Cl \end{array}$$

Suxamethonium (Succinylcholine, "Scoline").

It is probable, however, that this complication is not unfamiliar to those psychiatrists who regularly use suxethonium for E.C.T. modification.

Pharmacologically, both relaxants act identically causing depolarization of muscle membranes at the myoneural junctions, a process normally reversed by serum pseudocholinesterases. Enzymatic hydrolysis of suxamethonium and suxethonium is effected by these cholinesterases, more rapidly in the case of suxethonium than suxamethonium (13), which makes the former an ideal muscle relaxant for use with electroplexy (4), (29), (11).

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In spite of their advantages over other muscle relaxants used for electroplexy, short periods of apnoea following injections of Brevidil compounds have been observed by various workers. Blayney (4) reported apnoea lasting for 10 minutes following 30 mg. Brevidil "M" in a patient who was considered a poor risk, and Gillie and McNeill (15) referred to 3½ minutes apnoea after 100 mg. Brevidil "E". Fisher and Bannister (11) reported 5 minutes apnoea and Wolfers (41) 4 minutes apnoea after 90 mg. Brevidil "E", and the manufacturers (42) have referred to occasional instances of prolonged relaxation lasting beyond the usual 2 to 4 minutes.

Since there are no reports of prolonged apnoea following the use of the suxethonium brand of relaxants, the following cases are of interest, and indicate that suxethonium, like suxamethonium, is a powerful respiratory depressant, which may in certain circumstances produce not only apnoea but a profound degree of collapse.

Such a situation, occurring "out of the blue" during the routine performance of electroplexy, is an alarming experience for the doctor concerned, and sharply reminds us of the views of Sargant and Slater (34), who asserted that "to add pentothal and a relaxant to E.C.T. is to add two potential sources of danger each carrying its own risks of death".

Case 1

A male patient, F.A.W., was admitted in 1949, aged 53, suffering from a paranoid psychosis. A builder's labourer, he was in good physical health apart from a well-compensated mitral stenosis. His blood pressure was 170/100, but there were no other abnormal physical findings.

He had many fantastic grandiose delusions and ideas of reference which were mainly expressed towards the staff of the hospital. From 1949-51 he underwent several courses of "straight" electroplexy, resulting in marked temporary mental improvement, though he soon relapsed. No untoward effects were noticed after any of these treatments. In 1954 mass radiography revealed bilateral tuberculous infiltration of both apices and he received a course of chemotherapy. Throughout this time his general health remained excellent. In October 1957 he became increasingly boastful and paranoid, and imagined that his name and personal affairs were being broadcast over the radio.

Chlorpromazine 100 mg. t.d.s. was commenced with slight mental improvement, but this was omitted on the morning of treatment. On 1 November, 1957, he was given E.C.T. modified, in view of his chest condition. He had a well-relaxed fit, using the Ectonus technique, following 75 mg. Brevidil "E" given intravenously. No anaesthetic was used. Following this, his condition gave rise to increasing alarm and he became collapsed and pulseless, his blood pressure falling to 100/74. A fatal outcome was expected for he did not breathe spontaneously for approximately one hour, and when breathing recommenced it was initially shallow and jerky. He also developed bouts of auricular fibrillation.

Artificial respiration was performed manually, and with an oxygen and 5 per cent. CO_2 mixture under positive pressure using the Lucas breathing apparatus. Repeated intravenous injections of nikethamide were given (2 ml. in 10 ml. of saline) with little apparent effect, possibly because the dose used was too small. Unsuccessful attempts were also made to induce respiration by means of sub-shocks using the Ectonus machine, and to raise the blood pressure by intravenous injections of methedrine. Consciousness returned after one hour and 15 minutes, but apart from a slight headache the patient noticed no after effects. Blood taken for pseudocholinesterase estimation during the period of apnoea gave a value of 27 units. Following this single electric treatment the patient's mental condition improved markedly and he was able to return to employment in the hospital. A further pseudocholinesterase estimation on 27 June 1958 showed a value of 43 units. Liver function tests were regarded as normal, though the alkaline phosphatase was slightly raised (14 K units).

On 29 June the patient died suddenly while attending a church service. Post-mortem indicated that the cause of death was a small posterior myocardial infarct. There was no evidence of previous myocardial damage or mitral stenosis, though some thickening of the mitral valve was noted. The biapical tuberculous lesions were of minimal extent, and the liver appeared completely normal.

Case 2

A male patient, C.H.M., was admitted in August, 1955, aged 41, suffering from a schizophrenic psychosis. Physical examination on admission was normal and he appeared

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to be in excellent health. For the preceding eighteen months he had been developing ideas of reference and loss of concentration, and had noticed lack of manual skill together with troublesome aural hallucinations which gave a running commentary on his actions. He was obsessional and excessively preoccupied with his bodily functions.

Between April and November 1956 he received treatment with a variety of tranquillizing preparations (chlorpromazine, reserpine, suavitil, ritalin and meprobamate), but these had all been omitted by 26 November, when there appeared to be marked mental deterioration.

On 28 January, 1957, he received E.C.T. well modified with 75 mg. Brevidil "E". No anaesthetic was used, and no other drugs had been given except atropine gr. 1/100 ¼-hour beforehand. Following this treatment he did not breathe spontaneously for 45 minutes, and his pulse became irregular and varied in rate between 60 to 120 per minute. Artificial respiration was conducted manually throughout this period.

Afterwards he complained of no untoward effects apart from slight weakness and loss of sensation in the right leg. He was regarded as a case of hypersensitivity to Brevidil "E", and a number of pseudocholinesterase levels were performed between 28 January and 4 February which varied between 13·2 and 21·2 units. Liver function tests were carried out showing, total protein 6·7 G. per cent., albumin 4·7 G. per cent., globulin 2·0 G. per cent., albumin-globulin ratio 2·3/1, alkaline phosphatase 3 K units, urea 28 mg. per cent., total cholesterol 161 mg. per cent., free 53 mg. per cent., ester 108 mg. per cent., free-ester ratio 1/2·0, the low phosphatase level indicating a very slight degree of liver damage.

On 13 May the patient received a further E.C.T., this time unmodified in view of the previous experience, following which there were no respiratory complications. This caused marked mental improvement, and he has remained fairly well up to the time of his recent discharge.

Case 3

A male patient, R.W.J., aged 35, was admitted on 18 April, 1958, suffering from a schizophrenic psychosis.

Physical examination on admission was normal and he appeared to be in excellent health. There was no history of jaundice, and he had not at any time been exposed to chemical agents such as insecticides which are known to lower the pseudocholinesterases. Treatment with chlorpromazine 50 mg. t.d.s. was commenced on 19 April, but was omitted on treatment mornings.

On 21 April, he was given E.C.T. by the Ectonus technique using 50 mg. Brevidil "E". Atropine gr. 1/60 had been given 45 minutes previously, together with sodium amytal gr. 6 as he was apprehensive. The convulsion was well relaxed, but he became extremely cyanosed, and later white and shocked in appearance, and his pulse practically disappeared at the wrist. Altogether some 10 minutes elapsed before spontaneous respiration returned, which was initially shallow. During the apnoea artificial respiration was continued manually, assisted by oxygen given under positive pressure using the Lucas apparatus. The patient complained of no after-effects.

Because of this incident a further 8 treatments were given unmodified without any respiratory difficulties. After this he became increasingly hypochondriacal, and imagined his thoughts were under the direct control of wireless and television. He demanded to leave the hospital, and asserted that he would not consent to further E.C.T. unless he was given injections prior to treatment.

On 10 June E.C.T. was again given using 75 mg. Brevidil "E" following which he did not breathe for 4½ minutes. Blood taken during the apnoea contained 26 units of pseudocholinesterase. Three days later he received a further treatment using 50 mg. Brevidil "E" and this time the apnoea lasted 7½ minutes. The pseudocholinesterase was now 24 units. Liver function tests were reported as showing normal results.

He noticed no after-effects following these last two treatments, but insisted on handing in his notice of departure. Investigation of this case had therefore to be discontinued.

Discussion

It will be observed that all three patients had low serum pseudocholinesterase levels at the time and shortly after the respiratory difficulties were encountered, and that recovery was uneventful when unmodified E.C.T. was given. It is generally assumed that the distress (apnoea, coma etc.) is caused by the accumulation of acetylcholine in the body, because of cholinesterase inactivation produced by the muscle relaxant (suxethonium or suxamethonium), and that the removal of the drug by the pseudo-cholinesterase normally curtails its effect.

Mean normal values for pseudocholinesterase of adult serum have been

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given at 76·7 units (25), and range between 53 and 102 units (39), and at this laboratory anything over 45 units is regarded as a normal value. (Units refer to microlitres of CO_2 evolved per minute per ml. of serum or whole oxalated blood, at 30° C.) The pseudocholinesterase is estimated by means of the Warburg Manometric Technique, as described by Aldridge and Davies (1). This is a micro-method which requires careful handling and considerable experience, but the same operator can achieve a high degree of reliability. Values between 50 to 80 per cent. of the normal figure for a particular patient are usually symptomless, but mild symptoms are likely to occur when the value falls between 20 and 30 per cent. of normal, and severe symptoms when it lies between 5 to 10 per cent. of normal. Generally values below 30 units would be expected in prolonged comata, but it is emphasized that the serum pseudocholinesterase level is characteristic for each person. A drop therefore from 80 to 50 units may be just as significant as a fall from 50 to 30 units. The body, as in other biochemical balances, gets attuned to a certain level of acetylcholine, and shows symptoms when this level is appreciably altered, analogous to some diabetics who go into hypoglycaemic coma at blood sugar levels around 250 mg. per cent. Once inactivated, the pseudocholinesterase regenerates itself slowly, and may take a month or more to reach its previous level. In Case I, therefore, 43 units is likely to be the normal pseudocholinesterase level, taken six months following the prolonged coma.

It has been stated (2), that in the same individual a fixed dose of suxamethonium given at suitable intervals, produces a constant response, and in any given person the duration of the paralysis increases with increasing doses. (38), (9). With suxethonium, however, Blayney (4) noted no great difference in the duration of activity when the dose employed was just sufficient to control the convulsion, or large enough to produce complete paralysis, and it was therefore his practice to have his patients completely relaxed, using doses ranging from 55 to 140 mg. of the active cation of Brevidil "E". By contrast Hurley and Monro (22) noticed no symptoms when the dose was reduced in a patient who had previously shown "scoline apnoea", and did not therefore regard this complication as a deterrent to future modified E.C.T.

Evans *et al.* (10) and Bourne *et al.* (5) demonstrated an inverse relationship between the duration of apnoea following suxamethonium and the serum pseudocholinesterase, but this finding has not been universally confirmed, for Argent *et al.* (2) observed that the pseudocholinesterase level in six out of seven patients who exhibited prolonged apnoea after suxamethonium was not depressed to such an extent that the reduced enzyme level could be held solely responsible. Conversely Foldes *et al.* (13) noticed no cases of excessively prolonged apnoea following suxamethonium in a group of patients showing reduced cholinesterase activity due to liver disease.

Wolfers (40) reported a case of suxamethonium sensitivity in a patient with a normal pseudocholinesterase level, and imagined that susceptibility to the drug could vary in the same patient from day to day, suggesting that the subject was more complex, and that the duration of apnoea must depend upon factors other than pseudocholinesterases. These have been listed by Foldes and Rendell-Baker (12) and include:

1. Accumulation of succinyl monocholine. This results from the hydrolysis of succinylcholine (succinyl-dicholine) by the plasma pseudocholinesterases.

2. Central respiratory depression by succinylcholine.

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3. Central respiratory depression by general anaesthetic agents.

4. The production of succinylcholine "receptor block" rather than depolarization at the motor end plates. This would explain the beneficial results that sometimes attend the use of neostigmine in these cases of apnoea. (32), (33), (20).

5. Failure of redistribution of succinylcholine from the neuromuscular end-plates.

6. Persistent changes after removal of succinylcholine from the end-plates (refractory muscle).

7. Controlled respiration resulting in acapnia and exhaustion of the Hering-Breuer reflex.

The level of serum calcium which Irwin *et al.* (24) found to be lowered in animals with succinylcholine apnoea, may play a role which might profitably justify further investigation. The alteration of the patient's pH to the acid side resulting from acetylcholine accumulation leading to a slower rate of destruction of the drug (18), is likely to be an important factor in these conditions.

In these cases it seems probable that the serum pseudocholinesterase played an important part, since it was found to be greatly reduced in all three. In none was an anaesthetic (thiopentone) used, though in Cases 1 and 3 tranquillizers had been given up to the day before treatment, but in Case 2 they had been omitted for two months preceding E.C.T. It is known, for instance, that chlorpromazine and reserpine increase the risk of fatalities in patients undergoing E.C.T. and hence administration of these drugs should be suspended for a few days before commencing treatment (26). However, estimates of chlorpromazine urinary excretion indicate that a week or more may elapse before excretion stops after withdrawal of the drug. This means that tissue saturation with this drug may last for a considerable period, a point worth noting should there be any untoward effects in patients receiving muscle relaxants who have recently been treated with chlorpromazine.

It is also possible that in Cases 1 and 3, hyperventilation may have prolonged the apnoea by causing acapnia, though in Case 1 this was minimized by using an oxygen and 5 per cent. CO_2 mixture. The dangers of prolonging the apnoea brought about by relaxants by enthusiastic over-ventilation have been stressed by Gillie and McNeill (15), though in Case 2 this was minimized by using manual artificial respiration without oxygen.

It is emphasized that all three patients were apparently in good physical health when they received electroplexy. Low serum pseudocholinesterase levels have frequently been reported in patients described as "clinically ill", and Hodges (20) has suggested that pseudocholinesterase appears to be a critical index of the patient's physical state. Other causes of low serum pseudocholinesterase levels (amongst which are liver disease and insecticide poisoning) have been mentioned by Impastato and Berg (23) who also referred to low levels in 1 per cent. of normal subjects. Both Cases 1 and 3 had no history of liver disease and gave normal liver function test results, though in Case 2 mild liver disturbance was suspected, though there was no history or clinical evidence to corroborate this.

Forbat *et al.* (14) showed that low serum pseudocholinesterase levels might have a familial incidence, but it has not been found possible to investigate these patients from this aspect.

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We wish to emphasize that to encounter a patient who exhibits prolonged apnoea following the use of these muscle relaxants (suxamethonium, suxethonium) during the routine performance of electroplexy, is an alarming experience, especially when the operator is working single-handed as so often is the case. A recent questionnaire (43) (results to be published elsewhere) circulated to over 50 mental and teaching hospitals, showed that at 60 per cent., E.C.T. was given modified with pentothal and scoline, and that relaxants were used at 85 per cent. Suxethonium was used at some 22 per cent. of hospitals. In spite of this, at nearly 50 per cent. of the mental hospitals we approached, the services of a Consultant Anaesthetist were not available during the routine performance of modified electroplexy. This we feel must tax considerably the experience and resources of the Psychiatric Registrar, who is surprisedly called upon to resuscitate one of these near moribund cases exhibiting hypersensitivity to muscle relaxants, especially in the absence of a specific antidote.

Some points concerning prevention and treatment

The treatment of prolonged apnoea following suxethonium (and other depolarizing muscle relaxants) is complicated, for as yet no specific antidote exists (29), (4), but the following points may be of assistance to the doctor called upon to cope with this emergency.

1. The maintenance of adequate respiration. This is of prime importance. Measures should be taken to ensure that there is an efficient airway, and artificial respiration should be continued manually and with an oxygen and 5 per cent. CO_2 mixture under positive pressure, until spontaneous respiration occurs.

2. The use of a test dose of muscle relaxant given as a routine to all cases before modified electroplexy, to ascertain whether any undue sensitivity occurs. This had been described in the case of suxamethonium by Impastato and Berg (23), who suggested giving a test dose of 5 mg. scoline to all patients, and from the response calculating the optimum dose for muscle relaxation. However, in view of the findings in a patient reported by Calvert *et al.* (6), who only exhibited prolonged apnoea following a dose of suxamethonium in excess of 40 mg., and who showed no response to a test dose of 10 mg., it is doubtful whether this time-consuming procedure would be justifiable as a routine.

3. The transfusion of whole blood or serum to replace the pseudocholinesterase. This has been reported by Harrison *et al.* (19), and on other occasions, and Cowan (7) described a case who showed a dramatic response to fresh blood after failure of older blood. Pseudocholinesterase preparations ("Cholase") which artificially elevate the serum pseudocholinesterase, have been used with success. (6).

4. There have been a number of conflicting reports about the value of neostigmine in these cases. Blayney (4) maintained that this drug, being an anticholinesterase, would inhibit the *in vivo* destruction of suxethonium by cholinesterase and prolong its action, a view also shared by a number of writers in connection with suxamethonium and suxethonium (31), (37), (35), (18), (5), (10), (17), (28), (20), (36). However, Ruddell (32) claimed success with 6·0 mg. neostigmine in a patient who developed apnoea following succinylcholine and decamethonium, and recently reported (33) a further case in which there was an immediate return of respiration after 2·5 mg. of neostigmine had been given. Hodges (21) has drawn attention to raised end-plate resistance to depolarization by suxamethonium, and showed that it was independent of cholinesterase

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activity. Such "depolarization block" has been encountered in children, in cases of myasthenia gravis, carcinomatous neuropathy (8), and electrolyte imbalance, and may be induced by various drugs (particularly in those with an inherent tendency). E.C.T. with muscle relaxants should be avoided wherever possible in these subjects, though anticholinesterase compounds (neostigmine) may be helpful, and we believe should be given to all cases showing prolonged apnoea.

5. Opinions also differ concerning the value of nikethamide in the treatment of these patients. Harper (18) and Grant (16) used nikethamide without effect, but Barron (3) was enthusiastic about the use of this drug, if given in doses of more than 10 ml. intravenously, frequently finding that more than 20 ml. were required, and referred to it as "a simple and effective remedy". We would emphasize that no apparent success attended the use of nikethamide in Case 1, though we feel it should be given because of its general stimulant properties.

6. Reports have recently appeared (30), (27), concerning the effectiveness of intravenous PAM (Pyridine-2-aldoxine methiodide) as an antidote in cases of alkyl-phosphate poisoning. Synthetic alkyl-phosphates are used as remedies (isofluorophosphate (DFP)) or as insecticides (tetraethylpyrophosphate (TEPP)) parathion. This latter preparation is used extensively in Japan by workers spraying rice fields, who may in severe cases show respiratory depression and prolonged coma, together with other symptoms as a result of parathion poisoning. In these patients a low level of serum pseudocholinesterase is also observed. Previously treated with atropine, it has been shown that an intravenous injection of PAM (usual dose 1 Gm.) reverses some of the symptoms instantly, and results in reactivation of the pseudocholinesterase to normal levels. No side-effects have been reported so far following the administration of PAM, which may also be given orally.

Perhaps PAM is the specific antidote also in cases of respiratory paralysis following the use of muscle relaxants, associated with low serum pseudocholinesterase, and it is intended to try it out in any future examples of this condition that come to our notice.

SUMMARY

Prolonged apnoea following suxethonium (Brevidil "E"), a short-acting muscle relaxant used for modifying electrically induced convulsions, does not appear to have been reported previously, though numerous examples of this complication have been described following suxamethonium (succinylcholine, "Scoline"), a closely related chemical compound.

Three cases of prolonged apnoea following suxethonium (1 hour, 45 minutes and 10 minutes) are described, all of whom showed low serum pseudocholinesterase levels.

The causes of this complication are discussed in the light of this finding, together with the mode of action of the depolarizing group of relaxants to which suxethonium belongs. Other factors must be responsible for prolonged apnoea when the pseudocholinesterase levels are normal, and these are discussed.

The importance of apnoea following modified E.C.T. is stressed, since it has been ascertained that at approximately 85 per cent. of hospitals that give E.C.T. muscle relaxants are used. Suxethonium is used at 22 per cent. However, Consultant Anaesthetists are present at only 50 per cent. of mental hospitals during routine electroplexy sessions.

Some points concerning methods of prevention and treatment of prolonged apnoea are given.

It has been suggested that PAM (Pyridine-2-aldoxine methiodide) which successfully reverses some of the symptoms of alkyl-phosphate (Parathion) poisoning, and restores the serum pseudocholinesterase to normal levels, might act as a specific antidote in these cases of prolonged apnoea, and it is intended to try out this preparation in the future.

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NOTE

The Brevidil "E" used in these cases was supplied by Messrs. May & Baker Ltd. in ampoules containing 150 mg. of the total salt (100 mg. of the cation).

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