EFFECT OF CHANGES IN ELECTROLYTES, HYDRATION AND pH UPON THE REACTIONS TO MUSCLE RELAXANTS

BY

STANLEY A. FELDMAN

Department of Anaesthetics, Westminster Hospital, London

Claud Bernard (1883) postulated that, provided artificial ventilation was performed, it would always be possible to maintain life in a curarized animal, until ultimate reversal of the paralysis had occurred. This presupposed a very low toxicity for the drug and a complete reversibility of its action. Although this belief has been largely justified by both clinical practice (Rizzi, 1955) and animal experiments (Bovet et al., 1947, 1951), occasional reports of unusual and dangerous complications following the use of these drugs have cast some doubt upon this basic concept. There have been over thirty recorded deaths from "neostigmine resistant curarization" (Hunter, 1956; Foster, 1956; Burchell, 1957), and abnormally prolonged paralysis not conforming to this description has been reported following gallamine and d-tubocurarine.

It has been suggested that, in some of these patients, abnormalities of electrolytes, fluid balance or pH have contributed to the unusual response of the patient to the muscle relaxant drugs. A consideration of the pharmacological and physiological effects that such changes may have upon this description has been reported following gallamine and d-tubocurarine.

EFFECT OF ELECTROLYTES ON NEUROMUSCULAR TRANSMISSION

There are two principal sites where electrolytes may affect neuromuscular conduction.

Firstly, a block of neuromuscular conduction can be produced by electrolytes acting upon the postjunctural membrane of the motor endplate. They may so modify the resting membrane potential that it is no longer easily reversibly depolarized as a consequence of stimulation of a motor nerve.

Secondly, electrolyte disturbances may interfere with the normal production and release of acetylcholine by axons at the neuromuscular endplate.

THE MEMBRANE POTENTIAL

The effect of electrolytes on the postjunctural membrane.

The cell membrane which separates the intracellular fluid (ICF) from the extracellular fluid (ECF) carries an electric charge, the membrane potential. This results from its selective permeability and the uneven distribution of ions on either side of its surface. The magnitude of this potential may be predicted from the formula of Hodgkin and Katz (1949).

$$E = \frac{RT}{F} \log \left( \frac{P_K[K_I]_0 + P_Na[Na_I]_0 + P_Cl[Cl_I]_0}{P_K[K_E]_0 + P_Na[Na_E]_0 + P_Cl[Cl_E]_0} \right)$$

$R =$ gas constant; $F =$ 1 Faraday; $P =$ diffusion constant of ion; $i =$ ion concentration inside cell; $o =$ ion concentration outside cell.

At the postjunctural membrane of the neuromuscular endplate, neuromuscular conduction is effected as the result of changes in this resting potential brought about by a reversible shift of electrolyte ions. It is by modifying this resting potential that alterations in electrolyte concentrations affect the actions of the muscle relaxants.

Potassium is quantitatively the most important ion influencing neuromuscular transmission. Although gross alterations of sodium and chloride ions could theoretically produce a primary effect, within the tolerable physiological concentrations of these ions, their effect is usually secondary to a displacement of potassium from the intracellular fluid. Clinically symptoms only occur when these secondary changes have taken place. The magnitude of the transmembrane (resting) potential can therefore be considered to bear a direct relationship to the ratio of the intracellular to the extracellular potassium concentration.
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The normal range for \([K]_o\) is 3.9 to 5.0 m.equiv/l.

\[ \frac{[K]}{[K]_o} \]

this produces a resting membrane potential of 70 to 90 mV.

The effect of alterations in the potassium concentration upon the muscle relaxant drugs must be interpreted in the light of this ratio. The effects to be anticipated can be considered in the light of three possible circumstances:

A relative fall in extracellular potassium concentration.

A relative rise in extracellular potassium concentration.

A fall of both intracellular and extracellular potassium.

RELATIVE FALL IN EXTRACELLULAR POTASSIUM CONCENTRATION

A low plasma potassium concentration in the presence of a normal level of intracellular potassium will result in a cell membrane that is hyperpolarized. This increase in the resting potential of the postjunctional membrane at the neuromuscular endplate results in a resistance to the action of acetylcholine. As a result, a relative fall in extracellular potassium concentration will produce an effect clinically indistinguishable from that due to a small dose of antidepolarizing relaxant. This state is seen in familial periodic paralysis (Aitken et al., 1937). It occurs after an excessive loss of potassium, as occurs with mucus-secreting tumours of large bowel (Cooling and Marrack, 1957) and in renal disease (Mahler and Stanbury, 1956). It may also be produced by the shift of potassium from the extracellular fluid into the cells during insulin therapy for diabetic acidosis. Although the muscle weakness produced may be severe enough to produce respiratory insufficiency it is unlikely to produce complete paralysis of the respiratory muscles, as the potassium imbalance required would have to be so great that other vital functions, especially cardiac conduction, would be severely affected (Fourman, 1952).

It can be predicted that a relatively low plasma potassium will potentiate the actions of nondepolarizing muscle relaxants and antagonize the actions of the depolarizing agents. It may cause an apparent prolongation of the effect of curare-like drugs, as a neuromuscular block may be produced by the summation of a subclinical level of circulating drug and the effect of a low potassium; however, even under these circumstances a normal response to neostigmine would be expected.

RELATIVE RISE IN EXTRACELLULAR POTASSIUM CONCENTRATION

A high concentration of plasma potassium in the presence of a normal level of intracellular potassium will lower the resting membrane potential. This will facilitate the production of a muscle action potential, as the postjunctional membrane is in a less highly polarized state. If the extracellular potassium is raised rapidly, as can be achieved by a close intra-arterial injection of potassium, this alone produces a sufficient reduction of the resting potential to trigger off an action potential and cause muscular contraction. A low membrane potential will increase the endplate sensitivity to acetylcholine and depolarizing muscle relaxants. It will induce resistance to the antidepolarizing drugs (Wilson and Wright, 1936). Taylor (1962) estimated that raising the extracellular potassium from 5 to 7.5 m.equiv/l., reduced the effectiveness of d-tubocurarine by 50 per cent in the guineapig phrenic nerve-diaphragm preparation. Another effect of a low resting membrane potential is that it reduces the resistance of the cell to penetration by ionized drugs.

This condition occurs as a rare form of hereditary periodic paralysis (Van't Hoff, 1962), after the rapid administration of large quantities of old stored blood, which may have a potassium content of 50 to 60 m.equiv/l. at the time it is transfused, or as a result of the excessive administration of potassium salts. It occurs as temporary phenomena during extracellular acidosis, when potassium is displaced from inside cells by hydrogen and sodium ions (Berliner et al., 1951).
FALL IN BOTH INTRACELLULAR AND EXTRACELLULAR POTASSIUM

This is probably the commonest situation to be met with in clinical practice when a low plasma potassium is found. As would be expected, if there is a comparable fall in both the intracellular and extracellular potassium concentration the resting membrane potential will be relatively unaffected and the patient's response to muscle relaxant drugs will be normal. Oldfield (1956) reported a patient with a plasma potassium of 1.4 m.equiv/l. who had an uneventful anaesthetic using muscle relaxant drugs. The danger of this condition lies in its instability due to lack of reserve. In this state a relatively small shift of potassium into the cells, which would be easily tolerated by a normal patient, may precipitate hypokalaemic symptoms.

A deficiency of both intracellular and extracellular potassium may occur as the result of defective intake (Black and Milne, 1952) or excessive chronic loss either in the urine as in chronic pyelonephritis, nephritis associated with potassium loss, primary aldosteronism (Conn and Louis, 1956) and the excessive use of chlorthiazide. It may be due to chronic diarrhoea as in ulcerative colitis or to a pancreatic fistula.

It is difficult to interpret the effect of a low plasma potassium in terms of its effect on the neuromuscular junction without some appreciation of the total body potassium state, although this may sometimes be inferred from the clinical history. A further complicating factor is the relative instability of the separation of the intracellular and extracellular potassium. Shifts may occur due to metabolic and respiratory alkalosis (Robinson, 1961) moving potassium into the cells, whereas acidosis has the reverse effect. The administration of saline to a hypokalaemic subject tends to displace intracellular potassium from the intracellular fluid, whereas the administration of glucose may have the reverse effect. Allowance must also be made for the effect of dehydration and adrenal cortical stimulation upon the renal loss of potassium. It is not uncommon for patients to lose in excess of 80 m.equiv equivalents of potassium in their urine in the first day after major surgery. These effects may pass without producing symptoms in normal patients, but in one who has a low potassium reserve the effect may be pronounced. A case of recurarization following a rapidly falling extracellular potassium in the postoperative period has been recorded (Feldman, 1959). In another patient the effect of a low extracellular potassium coupled with delayed excretion of gallamine produced muscle weakness and respiratory insufficiency lasting for 6 days.

Foster (1956) suggested the possibility that muscle relaxant drugs may penetrate the blood brain barrier in the presence of a disturbed potassium balance and so cause an unusual action by virtue of a central nervous system effect. The exact site of the blood brain barrier is conjectural, but it is probable that, in the absence of extracellular fluid, the glial cells take on this function (Katzman, 1961). It would follow that the muscle relaxant would have to pass intracellularly in order to traverse this barrier. This would be most likely to occur when the cell membrane resting potential was low, as in the extracellular hyperkalaemic state. Most patients in which this possibility has been suggested had low plasma potassium concentrations and in some the condition appeared to be improved by an infusion of potassium salt. This would be contrary to what would be expected on the basis of this hypothesis.

Gray (1956) postulated that in the presence of a low serum potassium it might be possible that the blocking action of d-tubocurarine at the sympathetic ganglia might be enhanced as well. He suggested that this might be a possible cause of the hypotension observed terminally in “neostigmine resistant curarization.” The effectiveness of d-tubocurarine as a ganglion blocking agent varies from one ganglion to another and from one animal species to another, but it would appear that in order effectively to block ganglionic transmission and produce hypotension the potassium shift would have to be very gross, increasing the effectiveness of d-tubocurarine some 10 to 20-fold (Guyton and Reeder, 1950).

ELECTROLYTES ACTING BY DEPRESSING ACETYLCHOLINE RELEASE

Magnesium intoxication has been shown to cause a flaccid paralysis which is clinically similar to curarization. This effect summates with that of curare-like drugs and may be reversed temporarily.
by neostigmine. There is evidence that the principal action of magnesium is to depress the formation or the release of acetylcholine by the axon. A similar state may be produced by a very low level of plasma calcium (Brown and Harvey, 1940) although at this level of calcium deficit, cardiac dilatation and failure and muscle tetany are likely to be seen. A grossly raised serum phosphate level, like magnesium excess, also produces a curare-like block, also because of the depression of acetylcholine release. There have been no clinical reports of these conditions producing unusual reactions to muscle relaxants during anaesthesia.

**EFFECTS OF DEHYDRATION**

It is possible to influence the effect of muscle relaxants by alterations in the patient's state of hydration. This will produce a change in regional blood flow which may affect the distribution and elimination of the drug.

Churchill-Davidson and Richardson (1952) showed that the rapidity of the onset of the paralysis due to decamethonium and its duration could be influenced by blood flow; neuromuscular block appears earlier and wears off sooner in an excised limb. From these observations it is possible that if a muscle relaxant were administered to a dehydrated patient, its distribution to areas of vasoconstriction would be limited until adequate hydration was restored during the course of the operation, or postoperatively. This might result in apparent recurarization or an unusually prolonged action of the drug (Paton, 1958). The extent of these changes is modified by the great affinity of the neuromuscular endplate for the muscle relaxant (Chagas, 1962), so that this effect is only likely to be clinically obvious with very large doses of drug or in the presence of extreme vasoconstriction.

With the exception of suxamethonium and d-tubocurarine all the muscle relaxants in clinical use are dependent upon renal excretion for their ultimate removal from the body. It is probable that redistribution and fixation in the tissues limit the clinical effects of normal doses of these drugs and this appears certainly the case with d-tubocurarine. In the presence of severe dehydration redistribution will be affected and renal excretion may be absent. In these circumstances a normal dose of drug may cause an unusually prolonged effect and an excessive cumulative effect from subsequent doses may be anticipated. The occurrence of prolonged curarization and recurarization in the presence of extreme oliguria has been described (Fairley, 1950; Montgomery and Bennett-Jones, 1956; Wislicki, 1962).

**EFFECTS OF CHANGES IN pH**

The respiratory paralysis produced by the muscle-relaxant drugs necessitates the use of artificial ventilation. It is possible that the alterations of pH produced by the artificial ventilation may affect the patient's response to these drugs.

Creese (1949) showed that in an isolated muscle bicarbonate ions augment contraction. He attributes this to a shift of potassium into the cells. Conversely carbon dioxide accumulation produces a decrease in isotonic muscular contraction. If carbon dioxide is completely removed from the perfusing fluid, spontaneous muscular fasciculations occur. The effect of carbon dioxide is believed to be due initially to a change in intracellular pH and later due to a shift of potassium. Changes in the hydrogen ion concentration have little effect on normal neuromuscular transmission although a fall in pH potentiates the action of the anticholinesterase drugs (Gessell et al., 1944). A further possible site of action of changes of pH is at the nerve itself, for Lorente de No (1946) demonstrated that 5 per cent carbon dioxide raised the threshold for nerve stimulation.

Payne (1958) found that in the sciatic nerve-tibialis preparation of the cat, a rise in Pco₂ opposed the action of suxamethonium, decamethonium and gallamine, but enhanced the effect of d-tubocurarine. This unexpected finding cannot be adequately explained on the basis of the physiological changes which occur in the nerve, muscle or at the neuromuscular junction. Payne suggested that it might be an effect upon the drug itself, possibly as a result of influencing the ionization pattern. However, he was unable to obtain the same effect when the alteration in pH was achieved by acid infusion.

Changes in pH might affect the duration of action of the muscle relaxants by affecting their tissue binding and excretion. Utting (1963) has described an increase in tissue fixation of d-tubo-
curarine when patients and dogs were hyperventilated.

It has been observed that a fall in pH, either due to hypercarbia (Scurr, 1954) or metabolic acidosis (Brooks and Feldman, 1962), can produce an effect clinically similar to that of a small dose of a muscle relaxant, though by virtue of a central nervous system depression, for in such conditions respiratory insufficiency, paradoxical respiration, tracheal tug and muscular weakness may occur. Metabolic acidosis occurring after anaesthesia in a patient with a low serum bicarbonate can produce a syndrome indistinguishable from “neostigmine resistant curarization”, due to the effects of the fall in pH upon the central nervous system and circulation (Feldman, 1963).

CLINICAL ASSESSMENT

It is essential to be cautious in translating the changes in activity of the muscle relaxants produced under experimental conditions by alterations of electrolyte concentration, hydration and pH into reactions that may be expected in patients. The actions of the muscle relaxants depend upon the animal used and the actual muscle examined. Frequently the changes induced in experiments have been so profound, so localized or so prolonged that were they to occur in a patient, their actions upon the heart, brain and parenchymatous organs might be incompatible with life.

It is the fundamental nature of these effects rather than their extent that is important.

The separation of the effects of changes of electrolyte, fluid balance and pH is completely artificial. Electrolyte changes are invariably reflected in the state of hydration of the patient, whilst pH changes always produce secondary shifts of electrolyte. It is only when one considers the patient as a whole that the parts of this complex jigsaw can be put together. Only then can the effects of all these changes upon the reactions of the patient to the muscle relaxants be interpreted.

REFERENCES


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BOOK REVIEW


This book is part of the American Lecture Series and as a lecture would no doubt be excellent. It is certainly readable, and one hour will be found ample. The book consists of a brief review of the history of the subject, followed by a fairly detailed account of the techniques used by Dr. Smith. He gives a frank account of his difficulties and dispels any notion that electrical anaesthesia is just around the corner. Two attempts to anaesthetize human volunteers were abandoned at the request of the subjects after 40 minutes. It scarcely seemed necessary to add that full electronarcosis was not achieved! It is clear that inhalational anaesthesia would be hailed as a break-through if our practice were confined to electrical anaesthesia in its present state of development.

In this book one seeks in vain for any fundamental account of the underlying principles of electrical anaesthesia. Neither are we told about the difference between electrosleep and electronarcosis—a distinction which is stressed early in the book.

The book is written largely in the vernacular of the theatre and the laboratory, and many of the grammatical constructions will appear strange to English readers.

There is no index and a total of seventeen references seems meagre.

J. F. Nunn