The CENTRAL AFRICAN JOURNAL OF MEDICINE

Vol. 2 No. 5 MAY, 1956

CONTENTS

PUBLISHED MONTHLY, ANNUAL SUBSCRIPTION £2 2s. 0d.
Registered at the General Post Office as a Newspaper.

The Muscle Relaxants in Anæsthesia

BY

SIMON BADER, M.B., CH.B., D.A. (Rand)
Anaesthetist, Salisbury, S.R.

It may be stated that the use of the muscle relaxants represents a tremendous advance in anaesthetic practice. Prior to their introduction, muscular relaxation, especially in abdominal surgery, was brought about by chloroform or ether anaesthesia. But the complications following on the use of these agents were so frequent as to warrant the use of other methods, including spinal analgaesia, nerve block and infiltration with local anaesthetic substances in order to produce the maximum amount of muscular relaxation. The introduction of curare and the closely related group of drugs known as the "muscle relaxants" into anaesthetic practice have eliminated these techniques.

The term "muscle relaxants" includes a host of drugs employed to produce paralysis of skeletal muscle. These drugs are administered by intravenous injection and very rarely may be given orally (Myanesin).

To-day there are numerous muscle relaxants at our disposal. Many of them are still in the experimental stage and their efficacy has not yet been proved. This article, therefore, deals only with those preparations which are in common use in anaesthetic practice, having had an adequate clinical trial. These preparations include d-Tubocurarine chloride (Curare), Gallamine triethiodide (Flaxedil), Decamethonium iodide (Eulissin), Succinyl choline chloride (Scoline). Other preparations like D.M.E. (Dimethyl ether of d-Tubocurarine), Brevidil M and Brevidil E have had a fair trial, but have not been adopted universally as the other preparations. Laudolyssin, a very long acting relaxant, has recently been introduced and will be discussed later.

History

The history of muscle relaxants dates back to the sixteenth century, when Sir Walter Raleigh brought back to England from British Guiana samples of certain poisonous mixtures used by the South American Indian tribes on their arrow tips. In 1812 Charles Waterton gave an account of the South American poison "Wourali" and told of the famous story of the she-ass wounded by a poisoned arrow and restored to life by inflating its lungs rhythmically with a bellows, thus demonstrating that asphyxia was the cause of death from curare poisoning. In 1844 Claude Bernard, the famous French physiologist, demonstrated that curare exerted its paralysing action at the neuro-muscular junction, and in 1935 King, of the National Institute of Medical Research in England, isolated the active principle d-Tubocurarine from the crude curare extracts and found it to be a quaternary ammonium salt. In 1942 it received its first trial in anaesthesia (Grey and Halton), its purpose being to produce muscular relaxation in association with light plane general anaesthesia.

As a result of the discovery that the active principle d-Tubocurarine is a quaternary ammonium salt, this group of chemical substances was extensively investigated and several compounds were synthesised which have muscle relaxing properties. Chief of these was Flaxedil, a reliable medium acting relaxant discovered in 1947 by the Frenchman Bovet. Its mode of action, although of shorter duration, is similar to that of d-Tubocurarine.

Decamethonium iodide (C10, Eulissin, Syncurine) is another quaternary ammonium salt introduced about the same time. It has a very profound action of short duration and is about three to five times as potent as d-Tubocurarine. However, its action is unreliable and has often failed to produce muscular relaxation. It has consequently been dropped in favour of more reliable preparations.

Succinyl choline (Scoline) was introduced into anaesthesia in 1951. It is an extremely reliable ultra-short acting relaxant (three to four minutes), producing profound muscular relaxation. Its mode of action is different from that of curare and will be discussed later.

Very recently a new long acting relaxant has become available (Laudolyssin). Its action is similar to that of curare.

Mode of Action

Before discussing the effects of the various relaxants on the different systems, it might be useful to consider what happens when an impulse reaches the neuro-muscular junction to cause muscle contraction. As soon as an impulse travelling along a motor nerve arrives at the myoneural junction, acetylcholine is released from the nerve ending and depolarises (or renders electrically negative) the muscle end-plate. This current of depolarisation excites the muscle fibre and causes muscle contraction. In the meantime the acetylcholine which has been produced by this process is hydrolysed by an enzyme "Cholinesterase" which is present in

the nerve ending and end-plate. If this hydrolisation process by cholinesterase does not occur, the muscle fibre would be in a continual state of excitability and contraction. Curare and Flaxedil both decrease the end-plate potential, thus allowing cholinesterase to exert a longer action and make the muscle fibres unresponsive to any further impulses from the motor nerve. It follows that any preparation which will nullify the action of cholinesterase will restore the excitability of the muscles and make them contractile. Such preparations are Prostigmine (Neostigmin) and Physostigmine, which are known as anti-cholinesterases, since they destroy cholinesterase, allowing acetylcholine to accumulate at the myoneural junction and reinstitute muscular contraction. Prostigmin is therefore the physiological antidote to curare and Flaxedil.

Myanesin acts in a different manner. It does not prevent the passage of impulses across the myoneural junction. It acts, it is believed, on the basal ganglia of the brain and so reduces the excitability of spinal cord reflexes. Its action is therefore central as opposed to the other preparations which act peripherally. For this reason Myanesin is useful in the treatment of the convulsive diseases like tetanus and strychnine poisoning.

METHODS OF ADMINISTRATION

Most of the relaxant drugs are administered by intravenous injection, this producing an almost immediate effect and being complete in two minutes. Intramuscular injection has been used to obtain a prolonged effect after an initial intravenous dose of relaxant drug.

When contemplating using any of these relaxants, especially d-Tubocurarine of Flaxedil, it is advisable to inject a small dose intravenously and wait two minutes in order to detect any sensitivity towards the drug. The usual effect of a small dose is to produce a feeling of tiredness and drowsiness and weakness of the eyelids. Any ptosis or respiratory distress after a small test dose must be regarded as a sensitivity towards the drug, which must then be used with great caution or discontinued. Should there be no untoward reaction, the drug may be given in one of two ways:

(1) *Single Dose Method.*—By this method a large dose of the relaxant drug is injected. This will invariably produce apnoea due to paralysis of the intercostal muscles and diaphragm. An endotracheal tube or oro-pharyngeal airway is inserted and rhythmic inflation of the lungs is carried out until normal respirations return.

(2) *Fractional Dose Method.*—By this method the patient is anaesthetised in the usual manner and small doses of the relaxant drug are injected at intervals, to maintain abdominal relaxation with a minimal depression of the respiratory muscles.

This is the method of choice.

Scoline may be used as a continuous intravenous drip (0.1-0.2 per cent. solution), the rate of drops being regulated to the necessary amount of relaxation required. This may be obtained with very little respiratory muscle paralysis. This is an excellent method which I have used on numerous occasions, the great advantage being that the bowel is always contracted and the surgeon is not hampered by a large dilated loop of bowel interfering with his abdominal surgery.

Myanesin when administered intravenously is apt to cause haemolysis of the red blood corpuscles and has fallen out of favour as a general muscle relaxant. It may be given orally or via a stomach tube in the form of an elixir to control the spasms of tetanus, strychnine poisoning and status epilepticus.

The muscle relaxants may be used in combination with any anaesthetic technique. The favourite method is induction with sodium thiopentone (Pentothal) and nitrous oxide (oxygen) ether or cyclopropane maintenance. When anaesthesia has been established a small dose of relaxant is administered, sufficient to produce abdominal muscle relaxation, and small doses are repeated at intervals to maintain a prolonged muscular relaxation. It is common practice to inject curare or Flaxedil before pentothal because of their slower action, so that by the time the pentothal has been injected relaxation will have commenced. When using Scoline, however, the pentothal should always be given first, as Scoline produces a very rapid onset of muscle tremors and spasms which are very painful in the conscious patient. If, after the injection of the relaxant, there is cessation of respiration, the lungs are rhythmically inflated by means of the rebreathing bag until normal respirations return. It is essential to maintain adequate oxygenation during this period, otherwise the effects of anoxia will soon become established, with all the dangerous complications of cerebral anoxia.

Excretion

There is still some controversy as to the method of destruction of these agents in the blood stream. It is thought that some of the drug is detoxicated in the liver, but the majority is excreted unchanged by the kidneys. There is much proof of the renal excretion theory, as patients with impaired renal function show prolonged effects from normal doses of relaxant drug. Renal disease is therefore a relative contraindication to the use of these preparations. Scoline is broken down in the blood stream into choline and acetic acid and these products are excreted by the kidneys. Scoline may thus be used in renal disease.

General Effects of Relaxants

1. *Central Nervous System*

Normal doses of curare and other relaxants do not affect consciousness, but very large doses have been known to produce unconsciousness in an unanaesthetised individual. We also know that the arm-brain circulation time is about fifteen seconds, so that if a central effect is produced it would occur within fifteen seconds. However, the relaxant action of these drugs usually occurs in about ninety seconds, so it is unlikely that the action of the relaxant drugs is central in origin.

2. *Peripheral Nervous System*

The relaxants result in voluntary muscle paralysis through their action at the myoneural junction. The mechanism and physiology involved have already been discussed. Their action is confined to the motor elements in the nerve plate endings, but sensory effects are not produced by these drugs. This means that all painful sensations are appreciated by the unanaesthetised patient who has been curarised. It is thus essential that a patient be adequately anaesthetised when the relaxants are being used, for muscular paralysis will allow no movement to indicate that pain is being experienced. A "sleep dose" of pentothal, for example, is insufficient when used with a paralysing dose of muscle relaxant. Deeper anaesthesia, pentothal or other anaesthetic combination, is essential, as surgical shock can be hastened by too many painful stimuli reaching the cerebral sensory cortex.

3. *Autonomic Nervous System*

The muscle relaxants, especially curare and Flaxedil, exert a powerful blocking effect on both sympathetic and parasympathetic ganglia. This is one of the most important actions of these preparations, especially in abdominal surgery. Surgical shock is due to many factors, and in abdominal surgery the commonest cause of shock is traction of the mesentery resulting in pain stimuli reaching the sensory cortex via the splanchnic sympathetic nervous trunk and through the coeliac ganglia. Curare blocks sensory transmission at the synapses of these ganglia and thus prevents sensory sympathetic impulses from reaching the brain. Shock is thus prevented.

4. *Cardiovascular System*

The relaxants have no effect on cardiac muscle nor on the smooth muscle of the blood vessels. Often there is a fall in blood pressure if a large single dose of relaxant has been injected. This is probably due to the autonomic ganglion block with sympathetic system depression and subsequent fall in blood pressure. Another factor is the decreased venous return to the heart which accompanies muscle paralysis. With normal doses there is no appreciable change in blood pressure. Sometimes a rise in blood pressure occurs, but this should be regarded as a sign which requires some investigation, as it usually denotes that there is some degree of anoxaemia due to inadequate pulmonary ventilation accumulation of carbon dioxide, and a resultant raised blood pressure. It is this factor too which produces excessive bleeding in the wound, the surgeon often blaming curare for this, whereas the fault lies with the anaesthetist. A little assisted respiration will abolish the venous congestion, blow away the accumulated carbon dioxide and thus diminish bleeding by restoring the normal physiology of venous return to the heart. Flaxedil often causes tachycardia and this is probably due to its blocking action on the parasympathetic ganglia. It has no serious significance during anaesthesia.

5. *Respiratory System*

(a) *Pharynx.* — Pharangeal reflexes are abolished by all the relaxant drugs.

(b) *Larynx.*—The relaxants paralyse the laryngeal muscles and produce a widely open glottis with the vocal cords widely abducted. This allows easy intubation with endotracheal tube.

(c) *Trachea and Bronchi.*—Curare and Flaxedil may produce an alarming bronchospasm, most difficult to break. Cyanosis is pronounced and inflation of the lungs is carried out with the greatest difficulty. This condition results from the liberation of histamine in the tissues. It occurs more often after the larynx has been intubated and may be so severe that the endo-

tracheal tube must be removed and the lungs inflated with a face piece in position. Antispasmodics like amyl nitrite may have to be used in the rebreathing bag and atropine may have to be injected intravenously. Only in those cases which do not respond to this treatment should a little adrenaline be injected intravenously, but then with great caution.

(d) *Respiratory Muscles and Diaphragm.*— There is always some depression of respiration due to a degree of paralysis of the intercostal muscles, and with larger doses intercostal paralysis is complete, as may be the case with the diaphragm. If the respiratory depression is marked, assisted or controlled respiration by means of the rebreathing bag must be instituted to maintain normal cardio-respiratory physiology.

6. *Muscle*

The paralysing action on striated, voluntary muscle has already been discussed. Smooth muscle, as found in the abdominal viscera, blood vessels and uterus, is not affected by curare or Flaxedil. It has been stated that Eulissin does relax uterine muscle, so that if a relaxant is to be used for external version it would be the preparation of choice.

7. *Alimentary Tract*

These preparations all act on the crico-pharyngeus muscle and also relax the cardiac sphincter of the stomach. This latter effect may be very dangerous with a full stomach, the stomach contents regurgitating through the relaxed cardiac sphincter into the pharynx, with the danger of aspiration into the bronchial tree. There is no direct action on the smooth muscle of the bowel except in the case of Scoline, which drug gives rise to increased peristalsis possibly due to its acetyl-choline-like action with vagal stimulation effect.

ANTIDOTES

Curare, Flaxedil, D.M.E., Laudolyssin have an antidote in Prostigmine, which is an anticholinesterase and so allows acetylcholine to have a prolonged action. A large dose must be given to counteract the effect of these drugs, 1-5 mgm. being injected intravenously together with atropine gr. 1/100. The atropine is a counter-measure to the parasympathetic effects of the prostigmine, viz., salivation, slowing of the pulse and pulmonary oedema. It should not be necessary to have to use an antidote for curare if the timing between injections has been correct. However, the surgeon may decide to perform a shorter procedure than was at first anticipated, a big dose of curare may have been given and the patient may still be curarised at the end of the operation. In this instance prostigmine will have to be injected to terminate the action of the curare. The antidote to Eulissin is pentamethonium (C5), but in order to produce any effect a very large dose must be given, so large that there is a dangerous fall in blood pressure. Succinyl choline has as yet no antidote. In a recent article in the *British Medical Journal*, Hodges and Harkness have shown that serum pseudo-cholinesterase reduces the time of action of Scoline and this may in future be the antidote to Scoline.

CLINICAL USES OF THE RELAXANTS

1. *Abdominal Surgery*

Muscular relaxation in abdominal surgery has been the plaintive cry of surgeons struggling to close the abdomen with the patient pushing his intestines through the wound and the peritoneum retracted into the lumbar region with each respiration. Harsh words may be uttered by the surgeon in his desperate struggle (and even harsher words may be thought, but never spoken, by the anaesthetist!). However, the relaxants have come to the rescue of both, as it requires very light general anaesthesia in association with a moderate dose of relaxant drug to produce an ideal state for the surgeon, the peritoneum being sutured with the greatest of ease, and the surgeon, instead of abusing the anaesthetist, praises him for an excellently administered anaesthetic. Not only the surgeon benefits from the use of relaxants, but also the patient, who is far less shocked than he would be with deep ether anaesthesia.

2. *Thoracic Surgery*

It is in the field of thoracic surgery that the relaxant drugs have been proved to be of inestimable value. The ease with which they allow intubation of the larynx has revolutionised endotracheal anaesthesia. Bronchoscopy and oesophagoscopy have been made ridiculously easy (for the surgeon!) by the use of the short acting muscle relaxants, especially Scoline. Previously extremely deep ether anaesthesia was necessary to allow these endoscopic examinations. Surgery of the heart, lungs and great blood vessels in the chest has been made possible by the use of relaxants. The great problem of intrathoracic surgery has always been paradoxical respiration and shifting of the mediastinal contents subsequent to opening the pleura. This is due to the difference between the positive

pressure of the atmosphere and the negative pressure in the thoracic cavity, so that when the pleura is opened the lung on that side collapses and the mediastinum moves towards the opposite side on inspiration. Also on inspiration the affected lung becomes smaller as air is sucked from it into the healthy lung, and on expiration the affected lung will expand due to air from the healthy lung entering it. This is known as paradoxical respiration, and its danger lies in the fact that a lot of stale air is rebreathed into the healthy lung, resulting in an accumulation of carbon dioxide and inadequate oxygenation of the lung and body tissues. The "mediastinal flap" results in shock and, between these two conditions, the patient will rapidly deteriorate. To prevent these dangerous conditions, positive pressure anaesthesia is employed, and the relaxants are used to abolish all voluntary respiratory efforts by paralysing the muscles of respiration and so allowing rhythmical inflation of the lungs with a rebreathing bag.

3. *Obstetrics and Gynaecology*

It is doubtful whether any of the relaxant drugs cross the placental barrier. Tests with the drugs in animals did not demonstrate any in the foetus. Certainly, in practice, one never sees any ill effect in the baby from the injection of a relaxant into the mother. As a matter of fact, the best anaesthetic for Caesarean section in my opinion is induction with pentothal, maintenance with Cyclopropane and a little Flaxedil to stop abdominal straining and laryngeal spasm under the light general anaesthesia.

4. *Orthopaedic Surgery*

The relaxant drugs may be used to produce muscular relaxation for the reduction of fractures and for spinal manipulation. For this purpose the short-acting Scoline is the relaxant of choice, as its effect wears off within three to five minutes and, if a longer period of relaxation is required, further small doses may be injected at intervals.

5. *Ophthalmic Surgery*

The relaxants play an important part in the operation for squint in both adults and older children. The eye movements are very early paralysed by the relaxant drugs, so that relatively small doses are required to keep the eye quiet, as a moving eye will interfere with the surgeon's attempt to correct the squint. The relaxants are also useful in the operation for cataract when this is done under pentothal anaesthesia. One of the dangers after removal of a cataract under pentothal is the coughing which occurs when the patient comes round from the anaesthesia. Vitreous may be exuded and eventually the eye lost. The relaxants do help prevent laryngeal spasm which is responsible for this coughing bout.

6. *Plastic Surgery*

The relaxants help tremendously in the process of intubation for these cases. As electrocautery is so often used in plastic surgery a non-explosive anaesthetic technique is essential, especially for operations about the head, face and neck. This is easily done with light nitrous oxide, oxygen, trilene or pethidine, and intermittent doses of relaxant to maintain a smooth plane of anaesthesia.

AFTER EFFECTS

The only real after effects from the use of muscular relaxants is a prolonged paralysis of the intrinsic muscles of the eye, resulting in an inability to accommodate, so that one is unable to read clearly. However, this disappears within a few days.

Scoline is known to produce from moderate to severe pain in the muscles, especially the intercostal muscles, but this seldom lasts for longer than two days.

Since the use of the relaxants in anaesthesia, one has noticed an increase in the incidence of chest complications, namely, small areas of collapse at the base of the lung. This is possibly explained by the reduced volume of respiration and faulty aeration of areas of lung which remain collapsed even after normal respiratory volume has been restored.

OTHER USES OF THE RELAXANTS

1. *Shock Therapy*

The relaxants, especially the short acting ones, are used to prevent bone injury with the sudden convulsions of shock therapy. Fractures commonly occur as a result of extreme muscle spasm, and the relaxants prevent these.

2. *Convulsive States*

Status epilepticus, tetanus and strychnine poisoning have all responded to treatment by the relaxants. Myanesin is the preparation of choice, given either by mouth in the form of an elixir, if the patient is able to swallow, or by injection. If it is given by injection, a 2 to 5 per cent. solution should be used, for the standard 10 per cent. solution is likely to cause haemolysis and haemoglobinuria. In very severe cases the longer acting preparations may have to be given in the form of a drip to control

the muscular spasms. These cases should always be given oxygen and apparatus should be available for inflation of the lungs should this be necessary.

CONTRA-INDICATIONS

1. *Myasthenia Gravis*

In myasthenia gravis there is intense muscular weakness, thought to be due to lack of acetylcholine. The muscle relaxants will exaggerate this effect and should not be used. Curare may be used to confirm the diagnosis of myasthenia gravis. A small dose injected intravenously will produce a marked increase of muscle weakness.

2. *Severe Kidney Disease*

Relaxant drugs should be withheld from patients suffering from severe kidney disease, as delayed excretion can produce a prolonged paralysing effect.

3. *Marked Obesity*

Obese individuals have flabby abdominal muscles, so that muscular relaxation is easily obtained. Their breathing is of the thoracic type, the flabby abdominal muscles contributing very little to the respiratory movement. By giving them a muscle relaxant the intercostal muscles become weakened so that inadequate respiration results. Pulmonary inflation with the rebreathing bag becomes difficult because of the massive abdominal contents impeding the movement of the diaphragm, and these patients are consequently cyanosed until the effect of the relaxant wears off. I have found it far more satisfactory to maintain this group on nitrous oxide, oxygen, ether or closed circuit oxygen and ether rather than rely on the relaxants for depth of anaesthesia.

4. *Extremes of Age*

Old patients excrete the relaxant drugs very slowly, so a much smaller dose should be given than for the average adult. Children on the other hand can tolerate proportionately larger doses, but it is important to remember that with their faster circulation time the effects come on quickly and no time should be lost to institute assisted or controlled respiration to prevent cyanosis and anoxia.

Having discussed the contra-indications, it might be just as well to briefly summarise at this stage.

The essential *indications* for the use of these drugs are:

(1) To provide, with light anaesthesia, the muscular relaxation required for abdominal surgery.

(2) To allow controlled respiration for the prevention of mediastinal flutter and paradoxical respiration accompanying thoracotomy.

(3) To prevent laryngeal spasm during light plane anaesthesia.

(4) To potentiate other anaesthetic agents, so that only light anaesthesia may be maintained and a minimal quantity of these agents be used.

The relaxants have revolutionised anaesthetic practice, but to the inexperienced it must be emphasised that the relaxants are in no sense anaesthetic agents, and their use in anaesthesia demands careful balance between the anaesthetic agents employed and the relaxant drugs. The anaesthetist must see that there is adequate respiratory exchange to facilitate full oxygenation and allow elimination of carbon dioxide. He must also see that there is adequate expansion of all parts of the lungs, so that post-operative chest complications are minimised. It is quite obvious then that indiscriminate use of the relaxant drugs can lead to disaster in the hands of the inexperienced, and so bring unfair criticism of the efficacy of this excellent group of drugs which has become an indispensable aid to anaesthetists.

SUMMARY

The history, methods of administration, modes of action, antidotes, indications and contra-indications of the relaxant drugs have been discussed, as well as their effects on the various bodily systems.

Only those drugs in everyday anaesthetic practice have been reviewed.

REFERENCES

EVANS, T. F. (1949). *Modern Practice of Anaesthesia.* Butterworth.

GRAY, T. C. & HALTON, J. (1946). *Proc. R. Soc. Med.*, 39, 400.

HEWER, C. L. (1953). *Recent Advances in Anaesthesia and Analgesia*, 7th Ed. Blakiston.

HODGES, R. J. & HARKNESS, J. (1954). *Brit. med. J.*, 18th July.

MINNIT, R. J. & GILLIES, J. (1948). *Textbook of Anaesthetics*, 7th Ed. Livingstone.

MUSHIN, W. & RENDELL-BAKER, L. (1953). *Thoracic Anaesthesia Past and Present.*