MUSCLE RELAXATION IN SURGERY

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The almost routine use of muscle relaxant drugs in surgery today has undoubtedly brought many benefits, but the dangers of the use of these drugs are not obvious in any one man's experience. Recent work in the investigation of deaths associated with well over half a million anaesthetics showed that death occurred about five times more frequently after an anaesthetic incorporating a relaxant drug than when no relaxant drug was used.

It was Charles Waterton in 1812, thirty years before the introduction of nitrous oxide and ether as the first anaesthetic agents, who first investigated the paralyzing effect of the arrow poison of the South American Indians. He described an experiment on a she-ass which was kept alive by artificial respiration and recovered fully from a paralyzing dose of this drug.

Claude Bernard in 1844 showed by his classic experiment that the drug neither prevented the conduction of impulses by the motor neurones, nor impeded the contraction of the muscle itself. He concluded that its action was at the neuromuscular junction.

Muscular relaxation in surgical anaesthesia, however, continued to depend on the depth of anaesthesia obtained. The popularity of chloroform as an anaesthetic depended largely on the ease with which an adequate depth of anaesthesia was reached, and the quiet respiration which was associated with its administration.

The discovery of the local analgesic effect of cocaine in 1884 was followed in 1885 by the work of Halstead who described conduction anaesthesia. This provided muscular relaxation and analgesia of the area to be operated upon. The first planned spinal anaesthetic which gave complete relaxation of the abdominal musculature was given in 1898 by Bier of Kiel. Spinal anaesthesia was not used, however, owing to the toxicity of cocaine, until 1920, when the synthetic drugs were introduced for this purpose by Gaston Labat. From this time muscular relaxation in surgical anaesthesia was obtained by deep inhalation anaesthesia, by spinal anaesthesia, or by regional nerve block, usually associated with light inhalation anaesthesia.

In 1935 King in this country isolated the pure alkaloid dextro-tubo-curarine chloride in crystalline form from the crude arrow poison. In 1940 Bennett, and in 1941 Gray, reported the use of the paralyzing action of 'Curare' to mitigate the severity of the convulsions induced for the treatment of mental disease. It was Harold Griffith and Johnson of Montreal who in 1942 first described the use of a curare preparation for the specific purpose of obtaining muscular relaxation in twenty-five cases undergoing operative surgery. The effect they obtained from the use of their purified extract was found to depend entirely on the d-tubo-curarine chloride it contained.

Mode of Action

The transmission of nervous impulses at pre-ganglionic synapses of the sympathetic system and at post-ganglionic endings of the parasympathetic system, as well as at the neuromuscular junction was shown by Sir Henry Dale to be cholinergic. When an impulse reaches the motor end-plate of a striated muscle, acetyl-choline is released. The molecular configuration of acetyl-choline fits receptors on the limiting membrane of the end-plate. As a result the membrane becomes permeable to potassium ions from within and sodium ions from without. This alteration of the equilibrium of the motor end-plate is the depolarization which causes the spike potential. This in turn is propagated to the muscle as the action potential and is associated with muscular contraction. The acetyl-choline liberated is almost immediately destroyed by a tissue enzyme cholinesterase. This takes place in less time than the refractory period of the muscle. D-tubo-curarine and the curariform drugs block the action of the acetyl-choline at the receptors by themselves uniting with the receptors. The curariform drugs, however, do not make the limiting membrane permeable to the potassium and sodium ions, so no contraction takes place. The antidote to the curarizing drugs is physostigmine; this destroys the cholinesterase at the end-plates and allows the level of acetyl-choline to mount, which displaces the curariform drug and allows its normal action.

to take place. This anti-cholinesterase activity of physostigmine, or as is now used, neostigmine, takes place not only at the neuro-muscular junction of striated muscle but at all cholinergic nerve junctions. To avoid this parasympatheticomimetic action of physostigmine, which would cause bradycardia, salivation and colic, atropine is given.

The other group of drugs which are used as muscular relaxants and act at the myoneural junction are the depolarizing agents. These have the same effect on the motor end-plates as acetylcholine, causing depolarization, but they are not so rapidly destroyed by cholinesterase as is acetylcholine. Therefore there is a persistent depolarization, which lasts for a varying time and blocks the transmission of further motor impulses to the muscle. There is no antidote to the depolarizing muscle relaxants as the anti-cholinesterase, neostigmine, would only prolong the duration of the depolarization. Their action, however, is not quite clear cut. Cases of prolonged muscular relaxation following the use of suxamethonium have been ascribed to a low plasma cholinesterase. Recently Argent, Dinnick and Hobbigger have reported seven cases in which prolonged apnoea followed the use of suxamethonium. In six of these cases the plasma cholinesterase level was over 50 per cent. of normal. Zaimis has pointed out that these depolarizing drugs, suxamethonium and decamethonium, in dogs and horses have an action comparable to that of curariform drugs, and their effects are reversible by the use of neostigmine. It has also been suggested that in man these drugs may play a dual role in certain cases. To begin with acting by depolarization and later after large doses, or at an intermediate stage in their hydrolysis, acting as true curariform drugs.

An entirely different muscular relaxant is the drug Mephenesin. This does not act at the myoneural junction but centrally on the spinal cord and brain stem. It has been used intravenously to produce muscle relaxation. There have been numerous cases of haematuria and venous thrombosis following its use. It is now confined to use by mouth in cases of Parkinson's disease and to relieve the muscle spasm consequent upon upper motor neurone lesions. Its use in tetanus is recommended as it reduces the hyperactivity of the spinal reflex.

Use of the Relaxants in Clinical Practice

The introduction of the relaxant drugs has entirely changed the role of the classical anaesthetic agents. They are no longer relied upon to produce muscular relaxation but only to produce narcosis and analgesia. In a teaching hospital it is found

that 62 per cent. of all anaesthetics given are combined with a relaxant. This includes children in the first decade who are having ear, nose and throat operations, not requiring the use of a relaxant, and many cases where relaxants are not given in order to demonstrate to the students the classical signs of anaesthesia. These signs are all muscular and are not shown when a relaxant has been used.

The choice of a relaxant drug in any given case depends on many factors. Of these the most important are the extent, type and expected duration of the operation contemplated; the build of the patient, and the personal feeling and experience of the anaesthetist.

Dextro-tubocurarine chloride (Tubarine) is probably the most widely used relaxant in this country today. The dose, given intravenously, of 15 to 20 mg. produces adequate muscular relaxation in a 70 kg. man for 30 to 40 minutes. Atropine and prostigmine will reverse its action.

Gallamine-triethiodide (Flaxedil) is a synthetic curariform drug. That is, it acts by competition block. In a dose of 80 to 120 mg. it produces muscular relaxation for a slightly shorter period, 20 to 30 minutes. It is, however, associated with tachycardia in some cases.

Di-methyl ether of tubo-curarine (Metubine) is synthesized from d-tubo-curarine chloride and is two or three times more potent, weight for weight, than the original drug. Its dose is from 8 to 10 mg. and produces muscular relaxation of a slightly shorter duration.

Laudolissin is a synthetic curariform drug of a structure very similar to that of d-tubo-curarine chloride. It is about half as potent and the dose is from 30 to 40 mg. Its action, however, is very much slower in onset—up to five minutes—but it lasts much longer—up to 40 minutes.

Suxamethonium chloride (Scoline, Anectine); this is the commonly used suxamethonium halide. It is a depolarizing drug; its action is short, up to five minutes; the onset of paralysis is preceded by a phase of stimulation, when there is fasciculation of muscle, which is always seen to some extent. The dose is 50 to 100 mg., given intravenously, and there is no antidote. Cases have been reported where post-operatively the patient complains of subcostal pain and pain in large muscles.

Decamethonium iodide (Eulissin or Syncurine) is the other depolarizing relaxant which is in use. Its action is longer than that of suxamethonium, lasting some 20 minutes; paralysis begins three to four minutes after administration. The dose of decamethonium is 3 to 5 mg. There is no safe antidote to decamethonium; pentamethonium will reverse its effect at the motor end-plate, but

has itself such a severe ganglion blocking effect, with consequent fall in blood pressure, that its use is precluded.

In abdominal surgery the introduction of the relaxants has contributed to the fall from grace of spinal anaesthesia. In thoracic surgery the quiet lung is now obtained entirely by the use of muscular relaxants, coupled with very light inhalation anaesthesia. The short acting relaxants are of particular use for minor manipulations of orthopaedic surgery, for intubation in operations about the head and neck, where muscular relaxation would not otherwise be required and, of course, for electro-convulsive therapy, for which curare was first used.

The advantages of the use of muscular relaxant agents are manifest. No longer do we rely on what today would be considered a gross overdose of the classical anaesthetic agents to produce muscular relaxation. The advantage to the patients is that they are not soaked in a narcotic drug; the recovery time is decreased; post-operative nausea is reduced, and as a result of the early movement, post-operative chest complications and venous thromboses are minimized.

Contra-indications and Disadvantages

Myasthenia gravis is a contra-indication to the use of curariform drugs. If there is any doubt a small test dose should be given and its effect observed. These drugs should not be administered to any patient suffering from central respiratory depression. Also great care should be taken not to cause a central respiratory depression by such drugs as thiopentone or deep inhalation anaesthesia, as the resulting apnoea may be attributed to the relaxant drug and not to its true cause. For this reason young children who have often had heavy pre-operative sedation with the barbiturates are usually unsuitable for relaxant drugs. A very nice judgment of the lighter planes of anaesthesia is required. If the patient is too deep the advantages of the relaxant are lost. If the patient is too light it is possible that he may become conscious during the operation. Luckily post-operative amnesia helps to cover up such errors.

Any physiological response, such as rise in pulse rate or alteration in respiratory rhythm, is an indication that the patient is light and the anaesthesia should be deepened.

The clinical impression of anaesthetists in this country is that the post-operative mortality is less, and the post-operative morbidity is very definitely less. Recently Beecher and Todd have published the results of a most meticulous and methodical survey of deaths associated with anaesthesia over

a five-year period in ten teaching centres in the United States.

Total number of anaesthetics	599,500
Anaesthetics with relaxant	44,100
Deaths attributed to anaesthesia:	
Without relaxants	1 : 2,100
With relaxants	1 : 370

The deaths attributed to anaesthetics in which relaxant was stated.

	Cases	Deaths	Death Rate
Tubo curarine chloride	9,065	25	1 : 360
Decamethonium bromide	6,147	11	1 : 560
Succinylcholine chloride	699	3	1 : 230
Gallamine triethiodide	448	1	1 : 450
Dimethyl tubarine iodide	201	0	0

Their investigation must give rise to the greatest concern by all anaesthetists in this country. These results were also completely at variance with their own previous clinical impressions. All the patients were graded as to operative risk before surgery was undertaken. This did away with a tendency to put all patients who died, automatically, into the bad risk class. The difference in mortality rate was approximately the same whoever gave the anaesthetic: the staff anaesthetist, the resident anaesthetist, or a nurse anaesthetist. The difference in mortality was the same whatever the pre-operative condition of the patient was. The difference in mortality rate was approximately the same whatever the anaesthetic agent used, except in the cases of ether, where the figures were slightly worse. The cause of death was the most startling feature. They reported that 63 per cent. of the patients died from hypoxia, but 37 per cent. of the patients died from cardio-vascular failure, notwithstanding controlled respiration; this holds true for good and bad risk patients and in major or minor surgical procedures. They themselves offer no explanation for the high death rate associated with anaesthesia incorporating relaxant drugs, or for the high percentage of deaths from cardio-vascular failure. We have no evidence that these figures would not hold true for anaesthesia in this country.

The approach to anaesthesia in America differs from our own in that anaesthesiologists are intensely preoccupied with maintaining the normal pre-operative blood pressure. The use of intravenous infusions and the injection of vasopressor drugs, I found, were almost routine. It may be just possible that this combination of therapy with the relaxant drugs has some deleterious effect. Otherwise it must be assumed that the relaxant drugs are more dangerous than our clinical impression would have us believe. There may be

some action, other than that at the neuro-muscular junction, which is as yet unknown.

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CONTROL OF THE BLOOD PRESSURE AND CONTROLLED HYPOTENSION

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Control of the Blood Pressure during Anaesthesia

Blood pressure is the lateral pressure exerted by the blood on the vessel walls; our considerations are especially directed to the arterial system. The difference between systolic and diastolic pressure is the pulse pressure which depends on the stroke volume of the heart and the volume, elasticity and length of the arterial tree. In order to study the various factors influencing the arterial pressure, it is convenient to consider the mean pressure which is proportional to the product of the cardiac output and the peripheral resistance.¹

1. Cardiac Output

This is the product of the stroke volume and the heart rate and depends on the force of the heart and the cardiac filling.

(a) *The Force of Cardiac Contraction* affects the efficiency with which the heart muscles produce emptying. It depends on the initial length of the muscle fibres (Starling's law), so that an increased venous return leading to distension of the heart enhances the force of the beat. In a failing heart, however, overdistension occurs and increasing the venous pressure causes a further fall in output, conversely in such cases venesection may improve the circulation.

The force of the heart is also dependent on its nutrition and oxygen supply, which are affected by such factors as anoxaemia, the state of the coronary vessels and the arterial blood pressure. Excessive potassium ions cause increasing relaxation of the heart, finally bringing about arrest in diastole; for this reason stored blood is not advised for aortic transfusion during cardiac surgery.³⁸ Cardiac contraction is also influenced by body temperature and by nervous effects from

the vagus and sympathetic, it can be improved by humoral agents (adrenaline) and inotropic drugs, and is readily depressed by certain anaesthetic agents which produce dilatation.

(b) *Cardiac Filling:* This depends on the length of diastole and the effective venous pressure.

Venous pressure: The venous system accounts for 70 per cent. of the total volume of the vascular bed; it is evident that considerable circulatory adjustment can occur in this region. Surprisingly little is known of any venomotor mechanism: it is usually stated that there is insufficient muscle in the walls of the veins to produce any important effect. In the case of the larger veins it is probable that this thin layer of smooth muscle functions in a manner characteristic of hollow organs having a relatively thin wall compared with the size of the lumen, the purpose being maintenance of tone in order to allow considerable variation in capacity or filling with only slight changes in pressure.⁴ This tone is presumably regulated from the vasomotor centre: anaesthesia will diminish it, digitalis also can reduce venous pressure, noradrenaline can produce constriction of the veins and improve the venous return. A number of factors influence filling of the venous system, notably the blood volume.⁶ This may be varied in contrary directions by haemorrhage and transfusion. Closely connected with this is the state of the arterial bed, which accommodates a proportion of the blood volume and provides a through pressure to promote the venous return. The state of the body cavities, respiration, muscular activity and especially posture,⁹ mechanically influence the return of blood to the heart.

Apart from these effects on venous filling the venous pressure depends on the efficiency with which the heart empties the great veins. For this