THE MEDICAL JOURNAL OF
MALAYA,
Vol. XV, No. 1, September, 1960.

THE RELAXANTS

BY

JOHN NICHOLLS,

Anaesthetist, Lady Templer Hospital, Kuala Lumpur

Mode of action

Motor nerves to voluntary muscle terminate in motor end-plates applied to the muscle fibres. Between these two is a membrane with different electric potentials on each side of it.

When a motor impulse arrives at the end-plate, acetylcholine is released. As a result of this the electric potential difference across the membrane disappears ("depolarization") and an electrical wave spreads from it throughout the muscle, causing it to contract.

Curare blocks the action of the acetylcholine on the end-plate, competing with it for a place on the end-plate molecules, and so is called a "competitive blocker". Gallamine (Flaxedil) acts in the same way.

Scoline, on the other hand, causes depolarization of the end-plate membrane (hence the description "depolarizing" group of relaxants) and this does not produce, as one might expect, a sustained tetanic contraction of the muscle, but renders it inexcitable so that nerve impulses produce no effect.

Thus we have our two groups of relaxants — the competitive blockers like curare, and the depolarizers like scoline (suxamethonium).

Antidotes

Acetylcholine does not normally survive for long in the body, being destroyed by cholinesterase. If neostigmine is given this destruction is prevented and has the same effect as if a much larger quantity of acetylcholine were produced. Thus the acetylcholine is helped in its "competition" with curare and the effects of the latter are reduced.

It will be seen however, that the action of scoline, a depolarizer, will be helped by acetylcholine and thus by neostigmine, so that neostigmine is no antidote (quite the reverse) to scoline. Fortunately, the action of scoline is brief so that the lack of an antidote is less important. It is destroyed naturally in the body by " pseudocholinesterase " which may rarely be deficient in some people, so that artificial respiration for many hours may be necessary.

Doses required for complete paralysis and duration of action

The practice of using small doses and allowing the patient to breathe on his own is all very well in experienced hands but the respiration is already depressed under anaesthesia and the practice is very dangerous and best avoided. Either use the relaxants fully, with endotracheal intubation and "controlled respiration" or do not use them at all. All doses are intravenous.

Curare: (d-tubocurarine chloride, "tubarine", "curarine") has 10 mg to each cc and in a man of 10 stones about 30 mg (2 ampoules) will be necessary. The effect will last about 40 minutes on an average and if a longer period of relaxation is required a supplementary dose of about 1/3rd of the original dose should be given and then a similar period of paralysis should follow. D-tubocurarine works in about 4 minutes. Ether in particular, but also fluothane and other inhalational anaesthetics, will potentiate the action of curariform drugs and as little as 1/3rd of the usual dosage may suffice.

Gallamine ("Flaxedil") is supplied in ampoules of 80 mg (2 cc) and 120 mg (3 cc), the latter is about right for a 10-stone man. This will produce paralysis lasting for about 20-30 minutes and the supplementary doses should be about 40 mg when it begins to wear off. Again, less is required in the presence of ether, etc. The drug takes 2-3 minutes to work.

Scoline is supplied in ampoules of 2 cc containing 100 mg and usually this is given to a 10-stone adult though 75 mg is probably enough. The effect lasts from 5-10 minutes and may be prolonged by giving increments of 10-25 mg every 5-10 minutes through a Gordh or Mitchell needle or a syringe strapped in place. Paralysis which is particularly profound and so useful for intubation is heralded by muscle fasciculation and is complete in $\frac{1}{2}$-1 minute.

Use of Neostigmine

There are two strengths of solution but the commonest contains 2.5 mg to each cc. and this should be regarded as a "full" dose. Only on rare occasions when the improvement with 2.5 mg has been very good but some weakness remains do I exceed this dose and 5.0 mg must be regarded as rather dangerous dose. Usually I expect to finish the operation with the relaxant worn off, the last dose having been given an hour or more previously and then, when the patient is breathing (and usually awake) I give 0.5 – 1.25 mg to complete the recovery. All doses of neostigmine are preceded by atropine (both drugs being given intravenously) at an interval of at least two minutes. This is because neostigmine slows the pulse, lowers the B.P., causes increased salivation and overaction of the gut in addition to the desired effect and these parasympathomimetic effects are first blocked with atropine. About 1/100th grain preceding 1.25 mg of neostigmine is about right, but sometimes a supplementary dose, say gr. 1/200 will be necessary if the pulse slows to less than 60 per minute. If it is hard to strike a balance it is better to overdo the atropine.

"Controlled respiration"

This is usually performed by squeezing an anaesthetic bag and then relaxing it so that the pressure varies between 10 – 20 cm of water and atmospheric pressure — intermittent positive pressure respiration ("I.P.P.R."). The positive pressure phase compresses the heart, venae cavae and the vessels in the lungs themselves, reducing cardiac output, so it should be fairly "short and sharp" though not jolting and followed by a rest period $1\frac{1}{2}$ times to twice as long. If the BP falls for no obvious reason see that you are not breaking this rule. In controlled respiration the ventilation (volume of each breath rate of respiration) needs to be about twice as great as for the same patient breathing on his own, due

to the abnormal haemodynamics produced. Since hypoventilation is indisputably dangerous, and since the only effect of hyperventilation is alkalosis which clinically seems to do no harm in anaesthesia, see that you tend to err on the side of hyperventilation. Also, since washing out the CO_2 in this way removes the respiratory drive, and possibly for other reasons, less relaxant and less anaesthetic will be required. In chest operations lasting 2 – 3 hours I usually give one dose of curare at the beginning and then N_2O. O_2 only, except for pethidine occasionally; but of course tense abdominal muscles do not matter in such a case so long as the patient is not coughing or breathing. In abdominal operations it is often unnecessary to have absolutely flaccid recti after the initial exploration and for the closure 50-100 mg of thiopentone will usually give enough extra relaxation. If you must use 50-100 mg of scoline for this, do be sure that the curare or flaxedil has worn off or you may be faced with apnoea and be uncertain as its precise cause. On the other hand, to use scoline for intubation and then to continue with curare or flaxedil is almost universally accepted, and provided one awaits the first sign of destruction of the scoline (usually a twitch of the abdominal muscles as one squeezes the bag) before injecting the curare, is very safe.

During artificial respiration using relaxants very little addition to N_2O and O_2 is required, after the premedication and initial dose of thiopentone, to maintain unconsciousness and analgesia. Sweating or a rise in pulse and blood pressure may be due, for instance, to pulling on the peritoneum in an abdominal operation and small doses of pethidine will usually deal with this. 10-25 mg intravenously may be required every 15 minutes or so. Pain reflexes may also produce reddening of the sclera or tear-formation.

Sweating, a rise in pulse rate (followed by a fall), and a rise in BP may mean that the soda-lime is exhausted. When in doubt, change it. Also the closed circuit, with basal oxygen only, is not really safe and one should use, to be safer, high flows of gases even with soda-lime. I use at least 2 litres of N_2O to 1 litre of O_2 and often 4 litres to 2. The relaxant makes it possible to use higher proportions of oxygen if required. In a bad risk case and if anything goes wrong, say a severe fall in BP or cardiac arrest, use pure oxygen. Even if the patient shows some apparent awareness, he rarely remembers it in such cases.

Intubation

One may inflate a patient's lungs with a face mask and with the jaw held well up and forward to lift the tongue from the posterior pharyngeal wall; a pharyngeal airway may also be needed, either because the tongue is large or the nasal airway not patent. The latter is common and should be thought of, a lubricated airway should be on hand. After giving the relaxant, oxygen should be given in this way until relaxation is complete. Press down the emergency oxygen button or lever and ventilate the lungs, observing the movement of the chest wall. Then, with the back of the head on a small firm pillow, extend the head so that the face is looking towards you as you stand at the head of the table. Open the mouth, and guard the lips from being trapped with the forefinger and thumb of the right hand and gently insert the blade of the Mackintosh (curved blade) laryngoscope with the left hand until the tip rests between the epiglottis and the back of the tongue. Finally lift (do not lever) the lower jaw upwards so that the head appears to hang from the blade of your

laryngoscope. The cords, or at least the posterior half of them, should be clearly visible, and if they are not, do not continue struggling to get the tube in somehow, but get someone more experienced to check your technique. If your efforts are not immediately successful, give the patient a few breaths of oxygen from the mask before trying again: do not wait until he is cyanosed. If you are still unsuccessful do not be too proud to ask someone else to "have a go". And give some more oxygen while you are thinking about it. In many cases it would be wise to continue without intubation at all, rather than damage the cords. The only snags are that one may inflate the stomach, especially if a good airway is not maintained, and that stomach contents may regurgitate silently into the pharynx and so into the trachea.

There is bound to be someone who can coach you in the gentle art of intubation. Unless you have attained a reasonable proficiency you should not be using the relaxants. All the people who now appear so dextrous with a tube have had their red-faced clumsy moments. They will be glad to reduce the embarrassment for you and spare the patient a very sore throat indeed.

Two further points about intubation. If the tube goes down too far it will probably intubate the right main bronchus. An unsuspected one lung anaesthetic may cause carbon dioxide retention, even if oxygenation on a high oxygen atmosphere is achieved. Secondly, do not inflate the cuff more than is necessary to stop the throaty gurgle of escaping gases when the bag is compressed. Occasional decompression during the anaesthetic will give the sorely tried tracheal mucosa a better chance to survive uninjured.

Which relaxant to use?

I suppose the likely duration of the operation is the main consideration, but there are some special advantages and disadvantages you should know about.

Scoline produces post-operative aches and pains, particularly in the back; these are worse if the patient is soon ambulant. They occur in about 50% of cases. If scoline is used intermittently for a long operation, monocholine — a break down product — may be present in sufficient quantity to produce a curariform block and be perplexing and therefore dangerous. If the drug is used sensibly this is very unlikely to occur. After the initial dose, give small increments — say 10 to 25 mgm. — through an indwelling needle. Do not give them until there is some slight sign — abdominal movement, diaphragmatic twitches, swallowing, frowning, etc. — of returning muscle function. Record the time and the amount.

Intermittent scoline is especially applicable to the sick, aged patient with bowel obstruction or in any case where the normal electrolyte balance is disturbed. I once had to pump the bag for three and a half hours after using flaxedil in such a case. Avoid curare and flaxedil for them.

Scoline is suitable for babies, but the intubation of small children is difficult because of anatomical differences, quite apart from mere size. No matter how good you are at intubating adults, do not teach yourself

how to intubate the small fry by trial and error. Get some coaching. Scoline may be given intramuscularly, mixed with hyaluronidase. It is slower in onset and less certain. One can usually find a vein.

A slight rise of blood pressure and slowing of the pulse is common with scoline, especially after a second or third dose. It is not important.

The relaxation obtained with scoline is more profound — hence its use for intubation — than with normal doses of curare or flaxedil. Its rapidity and brevity of action are equally important.

Curare is the oldest of the relaxants and is probably still the most used. Its rather long action may be an advantage. There are two points one should bear in mind. Firstly there may be a release of histamine leading to bronchospasm. In a normal adult I use phenergan 50 mgm, well diluted with 10 cc. of water to counter this. Phenergan is usually successful in a minute or two. Secondly there is some ganglion blockade. This affects the sympathetic more than the parasympathetic so that a fall in blood pressure is not uncommon. Unless the positive pressure phase of ventilation is excessive the fall is seldom severe. It responds to raising the legs.

Flaxedil has one principal disadvantage. It raises the pulse rate and thus reduces the time for cardiac filling during diastole. It is a little unpopular for long operations on "cardiac" cases. However, it acts against the vagus, unlike curare, and therefore lessens the risk of bronchospasm. It is useful for asthmatics. If you must use a sub-apnoeic dose with spontaneous respiration (which is probably depressed enough already) 40 mgm of flaxedil is said to affect the diaphragm less than a corresponding dose of curare.

Incompatibility

It is best to wash each drug through the indwelling needle (I like Gordh's needle) or through the drip. Thiopentone and flaxedil are miscible. Thiopentone and scoline are not but I do wash thiopentone through with my dose of scoline. There is a form of curare which is miscible with thiopentone, but it is not so stable as the ordinary form. Pethidine is miscible with atropine and with phenergan, but of these three, only atropine is miscible with thiopentone. Apart from these examples, I always wash each drug through separately with water or saline.

Persistent apnoea

The operation is finished, the last dose of relaxant given an hour ago and nitrous oxide-oxygen has been replaced with pure oxygen for the last five minutes. Still the patient shows no sign of breathing on his own. What is to be done? Do not be in a hurry to do anything. Check the patient's colour blood pressure and pulse. Gently lift his eyelid and inspect his pupils for size, equality and expression. Sometimes you will be met by an enquiring wideawake stare from a patient who is quite satisfied with your respiration and just doesn't know it's all over. In such a case, speak to him reassuringly, put a sucker down the tube and withdraw both together after deflating the cuff and removing any packs.

Check your record of the anaesthetic drugs used and the time given. Do not attempt to neutralise any relaxants until the patient makes some movement. The character of this movement may give you some help. Has too much pethidine or morphine been used? If so ten mgm. of nalorphine (lethidrone) intravenously will antagonise one sixth gr. morphine or one hundred mgm. pethidine. But be careful; if more lethidrone is given than is required it will produce a morphine like effect itself. Pethidine depression of respiration commonly shows itself as a slowing of respiration, perhaps to 4 – 8 respirations per minute. There is little loss of depth of breathing and none of the jerkiness of relaxant action.

A gentle wiggle on the tube, or deflating the cuff will sometimes start the patient off swallowing and then coughing and breathing.

If you have over-ventilated and washed out the carbon dioxide, so that there is no urge to breathe, do not wait idly for the carbon dioxide to build up for minutes at a time. The patient needs a few good breaths of oxygen each minute while waiting. Don't allow the patient to stop breathing for a longer period than you yourself can hold your breath.

If you feel you must try something, 4 cc. nikethamide intravenously will often stir a sluggish patient. Once a few minutes of this expectant treatment has gone by, and if the patient's condition is otherwise satisfactory, you must resign yourself to continuing adequate ventilation with oxygen or oxygen and air until movement or respiration returns. When in doubt do nothing but this. Do not be prodded by some impatient colleague into giving neostigmine to a completely motionless apnoeic patient. You will only confuse yourself and may make matters worse if the apnoea is due to scoline sensitivity.

When the relaxant has worn off sufficiently, respiration will begin. Give the patient oxygen at first, not room air, until you are satisfied his breathing is adequate. It will not be smoothly flowing from expiration to inspiration but jerky, "rectangular" in form and accompanied by downward jerking of the thyroid on inspiration (tracheal tug) or even by sucking in of the upper chest. The patient may make weak, fretful, futile movements of his hands or head. This twitching is very characteristic. Intravenous atropine gr. 1/100th. followed by neostigmine 2.5 mgm. when the pulse has accelerated, will produce either complete return to normality or so much improvement that a suitable further dose to complete the cure can be estimated. If no improvement occurs, carbon dioxide retention may be present. Such retention not only causes coma, it also paralyses the myoneural junctions, mimicking curare. In the presence of a high oxygen atmosphere, carbon dioxide retention can easily occur without cyanosis. Even if the diagnosis is wrong the treatment of carbon dioxide retention can do no harm. Hyperventilate through fresh soda lime with a good flow of oxygen; 15 – 30 minutes of this will usually produce a great improvement. The patient may make vigorous attempts to take the tube out. Do not give him more anaesthetic drugs or relaxants. Continue the ventilation until his recovery is complete. Then watch him for half an hour or so. He may lapse into unconscious-

ness again. Do not take out the tube until you are quite sure he has recovered. Hyperventilate him again if he relapses. Two or three periods of half an hour each may be required. Finally see that he is carefully watched for the next 24 hours and any lessening of consciousness (the first sign) reported to you.

Is the patient safe to return to the ward?

In an uncomplicated case, the patient in good condition and breathing spontaneously, one should look for definite evidence that the relaxants have worn off before returning him to the ward. If he is conscious, ask him to open his eyes and to raise his arm off the bed. If he can do these things his muscular power is satisfactory. If he is half awake and his jaw is clenched so tightly that you cannot open it easily, or if he is pulling strongly at the sucker with his hand, obviously his muscles are working well. If he is unconscious he should be breathing smoothly, inspiration should be accompanied by chest expansion with no tracheal tug and the abdominal muscles should be tense before he returns to the ward. There should be no cyanosis.

Contraindications

There are hardly any contraindications to the use of a suitable relaxant. Myasthenia gravis must be remembered. If it is suspected, 2 – 5 mgm. curare or 10 – 20 mgm. flaxedil is given. These small doses will have no effect on a normal person. If myasthenia gravis is present the patient will be unable to open his eyes or may even require artificial respiration.

Emphysema is a common enough condition. It may make positive pressure respiration impossible, as in severe cases the lungs expand but fail to collapse. The chest stays inflated and fine wheezing is heard on expiration as air is trapped in the alveoli. Sometimes positive-negative respiration with a bellows may be more satisfactory although excessive negative pressure only makes matters worse by collapsing the bronchi. Broncho-dilators such as atropine, phenergan or aminophylline may help. If one appreciates the situation early, before the scoline for intubation has worn off, one can usually struggle on until breathing returns. If the pre-operative examination reveals emphysema, of course one should avoid artificial respiration, but a degree of emphysema which seems minimal in the ward may be much worse under anaesthesia. If the degree of emphysema is mild, beware of carbon dioxide retention under controlled respiration. It is easier to oxygenate such a man with high oxygen atmospheres than to remove his carbon dioxide because of the altered ventilation and circulation of blood in the emphysematous lung.