PHARMACOLOGY OF NON-DEPOLARISING MUSCLE RELAXANTS

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Non-depolarising muscle relaxants are commonly used during anaesthesia to provide relaxation for surgery, to allow mechanical ventilation and they are also regularly used in intensive care. This article describes the mechanisms by which the drugs work and also the differences between specific drugs.

Mechanism of action

Non-depolarising muscle relaxant drugs (NDMRD) compete with acetyl choline (ACh) molecules released at the neuromuscular junction to bind with the ACh receptors on the post synaptic membrane of the motor endplate. They therefore block the action of ACh and prevent depolarisation (or activation) of the muscle contraction process. Muscle groups differ in their sensitivity to muscle relaxants; ocular muscles responsible for opening and moving the eyes are the most sensitive followed by the muscles of the jaw, neck, limbs, intercostals and abdomen. The diaphragm is the least sensitive muscle, which is why patients undergoing surgery sometimes hiccup or breathe as an early sign that the relaxants are wearing off.

Non-depolarising muscle relaxant drugs also act on presynaptic receptors interfering with the entry of calcium which causes an inhibition in the release of ACh. Other drugs such as the aminoglycoside antibiotics (eg gentamicin) and volatile agents may also effect this mechanism and increase sensitivity to relaxants.

A variety of relaxant drugs are in use in different parts of the world. All produce profound muscle paralysis but have varying effects on the autonomic nervous system. None of the drugs cross the blood brain barrier as they are water soluble, polar molecules and therefore have no effect on the central nervous system. All non depolarising drugs should be used with care in patients suspected to be suffering with myasthenia gravis or myasthenic syndrome as patients with these conditions are extremely sensitive to their effects.

The commonly used drugs are summarised below.

Tubocurarine (Curare, d-tubocurarine) is a naturally occurring drug which takes about 3 minutes to act when given intravenously and lasts for 30-40 minutes.

Cardiovascular effects: Curare has no direct action on the heart but there is often a slight fall in the blood pressure secondary to a vasodilating effect via the sympathetic ganglia. In the presence of volatile agents the blood pressure fall may be greater. Care should be taken with this combination in hypotensive patients.

Respiratory effects: Curare has occasionally been associated with bronchospasm due to the release of histamine. It should be used with caution in asthmatic patients.

Histamine release may occur following the administration of curare and frequently presents as a red weal in the line of the vein which has been used for the injection. Problems associated with this reaction are very rare.

Placental transfer is not a feature of curare and the drug may be safely used in obstetrics.

Effect of metabolic abnormalities: Curare is potentiated by the presence of respiratory acidosis and hypokalaemia.

Distribution, metabolism and excretion: Thirty to forty percent is excreted unchanged in the urine and most of the remainder in the bile. In renal failure the drug is excreted effectively by the biliary route provided large or repeated doses are avoided.

Dose, administration and use: The initial dose

should be 0.3 - 0.6mg/kg followed by supplementary doses of 5mg when required (usually after 20-30 minutes). Neonates (less than 1 month old) are sensitive to curare and an initial dose of 0.3mg/kg is recommended.

Storage: Curare does not need to be refrigerated.

Gallamine (Flaxedil) is a synthetic (manufactured) drug which acts 1 -2 minutes after i.v. injection and lasts 20-30 minutes.

Cardiovascular effects: Gallamine produces an increase in heart rate, usually by 20-30 beats/minute due to an inhibitory action on the vagal supply to the heart. Blood pressure is usually unaltered unless bradycardia was previously present.

Histamine release is very rare.

Placental transfer: Gallamine is thought to cross the placenta more than other relaxants although it has been used successfully for Caearean section.

Effect of metabolic abnormalities: Gallamine is potentiated by alkalosis and antagonised by acidosis.

Distribution, metabolism and excretion : Gallamine is excreted almost entirely by the kidneys and should be avoided in patients with renal impairment.

Dose, administration and use : A dose of 1.5 - 2mg/kg is effective in 1-2 minutes and lasts for 15-30 minutes. Supplementary doses are usually 20 mg.

Storage: Gallamine does not require refrigeration.

Alcuronium (Alloferin) is a semi-synthetic muscle relaxant which has many similarities with curare. It is slightly shorter acting than curare.

Cardiovascular effects: After an i.v. dose there is frequently a slight fall in blood pressure due to vasodilation secondary to a degree of sympathetic blockade. This is occasionally accompanied by a tachycardia. Alcuronium is associated with a slightly higher incidence of anaphylactoid reactions than other non-depolarising muscle relaxants.

*Placental transfer***:** Alcuronium does not cross the placenta in appreciable amounts and has been widely used in obstetrics.

Distribution, metabolism and excretion: Most of the drug is excreted unchanged in the urine although some is also excreted in the bile. When used in patients with renal or hepatic impairment the dose should be reduced.

Effect of metabolic abnormalities: Mild acidosis or alkalosis does not alter the duration of action of alcuronium.

Dose, administration and use: Although there is some variation in requirements between patients an initial bolus of 0.2-0.3mg/kg is usually sufficient to provide relaxation for 20-40 minutes. Further increments should be with 15-25% of the original dose. It is potentiated by halothane. In children some anaesthetists recommend using doses of 0.125-0.25mg/kg. Always allow at least 20 minutes following the last dose before attempting to reverse the patient.

Storage: Alcuronium should be stored below 25 degrees centigrade and be protected from light.

Pancuronium (Pavulon) is a synthetic non-depolarising neuromuscular blocking agent.

Cardiovascular effects: There is a mild vagal blocking effect on the heart and an inhibition of the re-uptake of noradrenaline by the cardiac sympathetic nerves. These result in a rise in pulse rate of about 20% and an increase in the blood pressure of 10-20%.

Respiratory effects: Pancuronium can be safely used in patients with asthma.
Histamine release is not a problem.

Placental transfer is not a problem and pancuronium may be used in obstetric anaesthesia.

Distribution, metabolism and excretion: Sixty to eighty percent of pancuronium is excreted through the kidneys and the remainder is metabolised in the liver and excreted in the bile. It should be avoided if possible, in patients with renal impairment.

Effect of metabolic abnormalities: Acidosis potentiates pancuronium.

Dose administration and use: An initial dose of 0.1mg/kg will last 20-40 minutes. Increments of 1-2mg should be given as required. Always allow at least 20 minutes following the last dose before attempting to reverse the patient. Infants, children, elderly and obese patients may be more sensitive to pancuronium.

Storage: Pancuronium should be kept in a refrigerator.

Atracurium (Tracrium) is a short acting relaxant which is rapidly broken down by the body. This makes atracurium very predictable as it wears off rapidly compared to the longer acting relaxants.

Cardiovascular effects: Although atracurium produces few direct circulatory effects the absence of vagal blocking activity makes the patient vulnerable to bradycardias during anaesthesia. These episodes are commonest during ophthalmic (traction on the ocular muscles), ENT or abdominal surgery, particularly laparoscopy. The patient should be monitored closely and any bradycardias treated with atropine. Some anaesthetists give atropine or glycopyrrolate routinely at induction to prevent this problem.

Histamine release may occur with doses of atracurium greater than 0.6mg/kg. Histamine may also be released if atracurium precipitates in the syringe or vein. This may occur if atracurium is injected immediately after thiopentone.

Respiratory effects: In standard doses atracurium rarely causes problems with bronchospasm.

Placental transfer is insignificant and the drug is widely used in obstetrics.

Distribution, metabolism and excretion: Atracurium is broken down to inactive metabolites by ester hydrolysis and spontaneous Hoffman degradation. There is little change in its effects in patients with renal or liver failure. When used for long operations it is very predictable.

Dose, administration and use: A dose of 0.3-0.6mg/kg will provide relaxation for 20-40 minutes. Supplemental doses should be 5-10mg.

Contraindications: Atracurium precipitates (comes out of solution) in an alkaline pH and it should never be mixed with thiopentone. Always flush the vein with saline if using the two drugs at induction.

Storage should be in a refrigerator at 4 degrees centigrade as the drug deteriorates at room temperature.

Vecuronium (Norcuron) is a short acting relaxant prepared as a powder which is dissolved in sterile water immediately prior to use.

Cardiovascular effects are minimal although the potential problems listed under atracurium apply.

Histamine release is not a feature.

Placental transfer is minimal.

Distribution, metabolism and excretion : Vecuronium is excreted both in bile and urine. Its action is slightly prolonged in renal impairment.

Dose administration and use: An i.v. dose of 0.08 - 0.1mg/kg will produce relaxation for 15-30 minutes and supplemental doses should be 1-2mg.

Storage: Vecuronium powder does not need to be refrigerated.

General considerations in the use of muscle relaxants

Muscle relaxants are principally used to provide good muscular relaxation for surgery. When they are used respiration must be controlled via an endotracheal tube. A few general guidelines for the use of relaxants are listed below:

Always be certain that you will able to ventilate the patient by face mask before paralysing them.

If a rapid onset of action is required then suxamethonium should be used as it acts more quickly than any of the non-depolarising drugs. If a short duration of paralysis is required suxamethonium is

most suitable and may be given in repeated doses provided atropine is administered prior to the second dose of suxamethonium to avoid bradycardia.

Non-depolarising muscle relaxants take about one and a half to two minutes to act and you should allow time for relaxation to develop before attempting intubation.

The supplemental dose should be about 25% of the initial dose. Never attempt to reverse the relaxation until at least 15-20 minutes after the last dose of relaxant was given.

Never extubate a patient until you are certain that the paralysis has been reversed and they have adequate muscle strength to protect their airway and breathe. One way of testing this is to assess whether they are able to lift their head off the pillow for 5 seconds. Ensure that breathing is of adequate depth and frequency.

It takes some time before the larynx is able to protect the airway and so the patient is best placed in the lateral position for recovery.

If a nerve stimulator is available it can be used to monitor the degree of relaxation. However it is not essential and relaxants can be safely be used without a nerve stimulator by careful observation of clinical signs.

When muscle relxants are administered awareness is always a danger since a paralysed patient cannot move in response to pain. It is therefore essential to ensure that the depth of anaesthesia is adequate.

Relative costs of muscle relaxants (UK prices)

Drug	Ampoule size	Cost
Curare	15mg	71p
Gallamine	80mg	72p
Alcuronium	25mg	£1.86
Pancuronium	4mg	66p
Atracurium	50mg	£3.38
Vecuronium	10mg	£4.23
Suxamethonium	100mg	31-71p