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SKLETAL MUSCLE RELAXANTS. PERIPHERALLY ACTING SKLETAL MUSCLE RELAXAXANTS: NEUROMUSCULAR BLOCKERS AND SYNTHETIC COMPETITIVE BLOCKERS

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Abstract
Skeletal muscle relaxants (SMRs) are drugs that reduce the muscle tone either by acting peripherally at the neuromuscular junction (neuromuscular blockers) or centrally in the cerebrospinal axis or directly on the contractile mechanism. They reduce the spasticity in a variety of neurological conditions and are also useful in surgeries.

Keywords: curare, alkaloid, nicotinic receptor, tubocurarine, acetylcholine, anticholinesterase, histamine, respiratory paralysis.

Introduction

Curare was used by the South American Indians as arrow poison for hunting wild animals because curare paralysed the animals. On extensive research, the active principle from curare, tubocurarine was identified. d-Tubocurarine (d-Tc) is the dextrorotatory quaternery ammonium alkaloid obtained from the plant Chondrodendron tomentosum and plants of the Strychnos species (l-tubocurarine is less potent). Several synthetic agents have been developed. All these are quaternary ammonium compounds because of which they are not well absorbed, do not cross the BBB and are quickly excreted.

Non-depolarising blockers bind to NM nicotinic receptors on the motor end plate and block the actions of acetylcholine by competitive blockade. These compounds slowly dissociate from the receptors and transmission is gradually restored. Thus, the action of d-Tc is reversible. Increasing the concentration of the agonist acetylcholine at the NMJ also overcomes the blockade. This can be done by the administration of anticholinesterases like neostigmine.

On parenteral administration, tubocurarine initially causes muscular weakness followed by flaccid paralysis. Small muscles of the eyes and fingers are the first to be affected, followed by those of the limbs, neck and trunk. Later the intercostal muscles and finally the diaphragm are paralysed and respiration stops. Consciousness is not affected throughout. Recovery occurs in the reverse order, i.e. the diaphragm is the first to recover. The effect lasts for 30–60 minutes. In high doses tubocurarine can block autonomic ganglia and adrenal medulla resulting in hypotension.

Histamine release: Tubocurarine can cause histamine release from the mast cells leading to bronchospasm, increased tracheobronchial and gastric secretions. Histamine release also

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contributes to hypotension. Some of the other NMBs also release histamine. They release histamine by a direct effect on the mast cells.
Tubocurarine and other NMBs are quaternary ammonium compounds, hence not absorbed orally. They are given either IM or IV.
Adverse Reactions Respiratory paralysis and prolonged apnea—patient should be given artificial ventilation. Neostigmine or edrophonium may be used to reverse the skeletal muscle paralysis. Hypotension is due to ganglion blockade and histamine release.
Flushing and bronchospasm due to histamine release by tubocurarine; this is not seen with newer agents.
Treatment of toxicity: Neostigmine and edrophonium reverse the skeletal muscle paralysis and are the antidotes in curare poisoning. Antihistamines should be given to counter the effects of histamine. Neostigmine/edrophonium may be used to reverse the NM blockade after the surgical procedure is completed. An antidote sugammadex has been introduced for overdosage of rocuronium and vecuronium. Sugammadex binds to rocuronium, chelates and quickly reverses its effects. The complex is excreted in the urine. It can also chelate other NMBs like pancuronium to some extent.
Synthetic Competitive Blockers: pancuronium, atracurium, vecuronium, gallamine, doxacurium, mivacurium, pipe curonium, rapacuronium, rocuronium are synthetic NMBs.
They have the following advantages over tubocurarine: Less histamine release
Do not block autonomic ganglia, hence cause less hypotension Spontaneous recovery takes place with most of these drugs Hypotension is due to ganglion blockade and histamine release.
Some are more potent than tubocurarine
The newer agents rapacuronium and rocuronium have a rapid onset of action. Hence, they can be used as alternatives to succinylcholine for muscle relaxation. When so used, rapacuronium can cause severe bronchospasm before endotracheal intubation. Rocuronium does not cause hypotension, tachycardia and is fast acting. Atracurium can be safely used in patients with renal impairment because it is degraded spontaneously and to a small extent by plasma esterases by Hofmann elimination and does not depend on the kidney for excretion. It is partly metabolised in the liver. Laudanosine, a metabolite of atracurium, can cause seizures and increases the requirement of the anaesthetics.
Cisatracurium is an isomer of atracurium. Advantages: – Forms lesser laudanosine– Lesser histamine release when compared to atracurium.
Therefore, cisatracurium is now preferred over atracurium.
Mivacurium is a short-acting neuro muscular blocker with a slow onset of action. It is rapidly metabolised by plasma cholinesterases, hence short acting. It causes significant histamine release.
Tubocurarine, doxacurium and gallamine have a slow onset (about 5 minutes) but long duration of action (30–120 mins). Pancuronium, vecuronium, atracurium and cisatracurium have intermediate onset (2–4 minutes) while rapacuronium and rocuronium have fast onset of action (1–2 minutes).
Gantacurium is a new non-depolarising neuromuscular blocker under clinical development that has a rapid (~1½ min) and short action (~10 mins). Its actions can be completely reversed by administration of cysteine since it is metabolised by adduction to cysteine. It appears to be a

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promising NMB. Transient hypotension, tachycardia and flushing are related to histamine release which is dose dependent.

Tubocurarine causes histamine release, ganglion blockade (resulting in hypotension) and its muscle relaxant effect needs to be reversed with drugs. Hence, it is not used now. The synthetic compounds are preferred. Alcuronium and gallamine are also not used.

In conclusion, Skeletal muscle relaxants must be used only by trained doctors because inadvertent use can prove fatal. Peripherally acting SMRs do not affect the consciousness, hence awareness may be a horrifying experience to the patient-adequate precautions should be taken.

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