Neuromuscular blocking agents and reversal agents

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Abstract

The neuromuscular junction consists of the motor nerve terminal, the synaptic cleft and post-synaptic nicotinic receptors on the motor end-plate of striated muscle. Neuromuscular blocking drugs are categorized into depolarizing and non-depolarizing agents. They are structurally related to acetylcholine (ACh), containing at least one positively charged quaternary ammonium radical that binds to the nicotinic receptor. Depolarizing agents (e.g. suxamethonium) act as agonists like ACh at the nicotinic receptor, but cause a more prolonged depolarization of the motor end-plate, thus rendering the ion channel insensitive to further action potentials. Non-depolarizing agents, in contrast, compete directly with ACh for nicotinic receptor binding sites and prevent neurotransmitter–receptor binding. These are either benzylisoquinoliniums (e.g. atracurium) or aminosteroids (e.g. rocuronium). Once recovery has commenced, neuromuscular block can be reversed with anticholinesterases (e.g. neostigmine). In contrast, the novel cyclodextrin sugammadex can be used to reverse any degree of neuromuscular block produced by rocuronium or vecuronium.

Keywords Depolarizing agents; monitoring; neuromuscular block; neuromuscular blocking agents; non-depolarizing agents; pharmacology; physiology; reversal agents

Royal College of Anaesthetists CPD Matrix: 1A02

The introduction of neuromuscular blocking agents (NMBAs) into anaesthetic practice in the 1940s revolutionized airway management and surgical technique. Prior to their use, muscle relaxation was attempted by administering deep inhalational anaesthesia, subjecting patients to profound, and occasionally fatal, cardiopulmonary compromise. The advent of NMBAs allowed the anaesthetist to reduce the depth of anaesthesia, manage the airway for prolonged surgery, abolish reflex muscle activity and optimize patient positioning.

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Learning objectives

After reading this article, you should be able to:

- describe neuromuscular junction physiology
- list examples of neuromuscular blocking agents and reversal agents
- compare benzylisoquinoliniums with aminosteroids

Neuromuscular physiology

The neuromuscular junction (NMJ) consists of the motor nerve terminal, the synaptic cleft and post-synaptic nicotinic receptors on the motor end-plate of striated muscle. The synapse is 60 nm wide. The neurotransmitter acetylcholine (ACh) is synthesized, stored and released from the pre-synaptic terminal. The Ach receptors are situated on the post-junctional folds of the motor end-plate. These receptors are ion channels that open when ACh binds to them at specific binding sites – the α subunits. The synapse and post-junctional folds also contain the enzyme, acetylcholinesterase, responsible for the breakdown of ACh into choline and acetate. Choline is taken up across the nerve membrane for reuse and further neurotransmitter synthesis. Before muscle contraction, an action potential is propagated down the motor axon, depolarizing the pre-junctional nerve end-plate. This triggers the release of ACh from the pre-synaptic membrane into the synaptic cleft. Acetylcholine binds to the Ach receptors, causing a conformational change in the structure of the ion channels, resulting in their opening. In the open state, Na^+ influx through the ion channels causing depolarization of the motor end-plate membrane. Potassium ions exit causing repolarization and a return to a negative membrane potential. The summation of this process through a large number of receptor channels allows the generation of muscle contraction. Neuromuscular blocking agents prevent neuromuscular transmission by ACh receptor blockade, whereas reversal agents such as neostigmine enhance it by antagonism of acetylcholinesterase.

Neuromuscular transmission monitoring

Clinical assessment of neuromuscular block can be achieved during anaesthesia by electrical stimulation of a peripheral nerve, and should be undertaken whenever non-depolarizing NMBAs are used. It provides only a crude estimation of the degree of ACh receptor block. A supramaximal current of up to 60 mA applied for 0.2 ms to, for instance, the ulnar, facial or lateral popliteal nerve will produce a brief contraction in the innervated muscle. The response is assessed clinically by visual or tactile means. Supramaximal stimulation resulting in simultaneous depolarization of all the nerve fibres is essential to eliminate variation in muscle fibre response.

A single twitch (0.1–0.2 ms) stimulus is tolerated by the awake patient, but is of limited value. The train-of-four (TOF) twitch response is a series of four pulses at 2 Hz. The ratio of the amplitude of the fourth to the first twitch is called the train-of-four ratio, and is used clinically to assess the degree of block. It has the benefit of not requiring a control value to be obtained. At least the second twitch of the TOF should be detectable before recovery is induced with an anticholinesterase.

Please cite this article in press as: Farooq K, Hunter JM, Neuromuscular blocking agents and reversal agents, Anaesthesia and intensive care medicine (2017), http://dx.doi.org/10.1016/j.mpaic.2017.03.007

Neuromuscular blocking agents

Neuromuscular blocking drugs are categorized into depolarizing and non-depolarizing agents. They are structurally related to ACh, containing at least one positively charged quaternary ammonium radical [$-N^+(CH_3)_3$] that binds to the nicotinic receptor. Depolarizing agents act as agonists like ACh at the nicotinic receptor, but cause a more prolonged depolarization of the motor end-plate, thus rendering the ion channel insensitive to further action potentials. Non-depolarizing agents, in contrast, compete directly with ACh for nicotinic receptor binding sites and prevent neurotransmitter- receptor binding. Figure 1 shows the structure of acetylcholine and some of the NMBAs described in this article.

Depolarizing agents

Suxamethonium (succinylcholine) was introduced in 1951. It is the only depolarizing agent available for use in the UK. It is structurally similar to two molecules of ACh (Figure 1). Administration results in nicotinic receptor opening, Na^+ influx and initial depolarization of the post-junctional membrane. This produces brief, irregular muscle contractions termed fasciculations. A state of persistent depolarization then occurs, known as phase I block. Repeated or prolonged administration of suxamethonium produces a state of phase II block or desensitization. The features of phase II block are similar to non-depolarizing blockade: fade of the TOF and twitch response, and reversibility with neostigmine.

The onset of muscle relaxation following suxamethonium 1–1.5 mg/kg occurs within 60 seconds, and clinical recovery occurs in 5–10 minutes. Suxamethonium is metabolized by the enzyme plasma cholinesterase, with some breakdown by non-specific esterases. The drug undergoes very little hepatic metabolism, with 10% being excreted unchanged in the urine. In some individuals, plasma cholinesterase is structurally abnormal because of inherited factors, or reduced in concentration because of acquired factors (pregnancy, hypothyroidism, hepatic failure). These deficiencies will prolong its duration of action. The advantages of suxamethonium compared with non-depolarizing NMBAs are its faster onset, greater degree of relaxation and short duration of action. It is therefore suitable for use in rapid-sequence induction. There are, however, several disadvantages to this drug, including hyperkalaemia, ocular hypertension, raised intracranial pressure, myalgia, malignant hyperthermia, suxamethonium apnoea, anaphylaxis and its muscarinic effects such as bradycardia. Thus, suxamethonium is far from an ideal neuromuscular blocking agent; however, despite considerable effort, no suitable alternative can as yet rival its rapidity of onset.

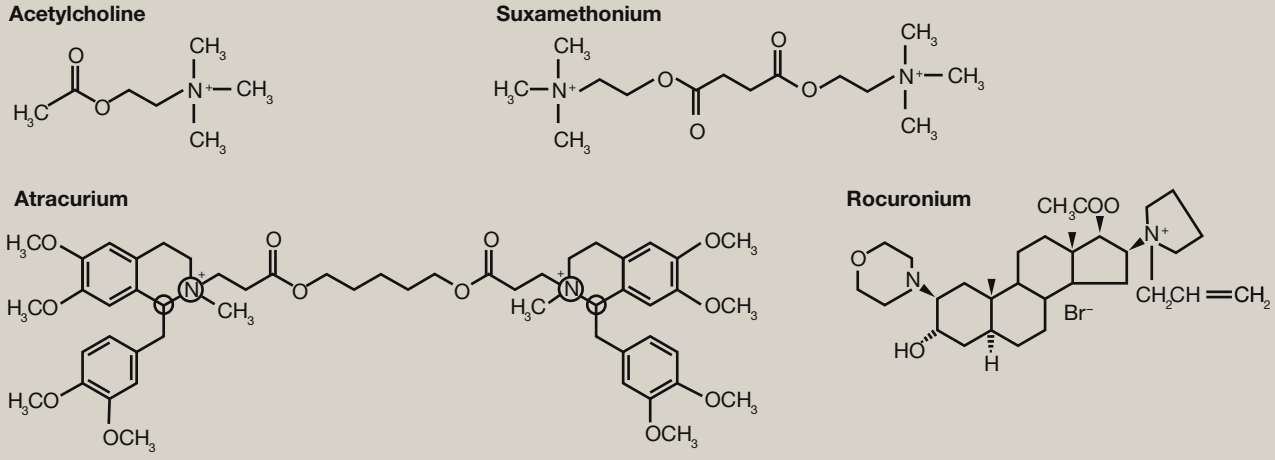
Non-depolarizing agents

The non-depolarizing NMBAs reversibly bind to the α subunits of the ACh receptor, competing with ACh for receptor activation. No initial contraction takes place as the structural conformation of the ion channel remains unaltered. Non-depolarizing NMBAs in current use are either benzylisoquinoliniums derived from tubocurarine, (atracurium, mivacurium, cisatracurium) or aminosteroids (pancuronium, vecuronium, rocuronium).

A new series of fumarate compounds belonging to the family of tetrahydroisoquinoliniums (gantacurium, CW002 and CW001) are currently undergoing clinical trials in the USA. They are designed to have both a rapid onset and short duration of action.

Benzylisoquinoliniums: *Atracurium* is an intermediate-acting bisquaternary ammonium compound, first used in 1980. It exhibits ten different stereoisomers, resulting from four chiral centres (Figure 1). This agent is metabolized by two pathways: Hofmann degradation (60%) and ester hydrolysis (40%). Hofmann degradation is the spontaneous breakdown of compounds at a given temperature and pH. Atracurium is stable at pH 4 and at 4 °C, but at body pH and temperature it spontaneously breaks

Structures of acetylcholine, suxamethonium, atracurium and rocuronium



Suxamethonium (succinylcholine) is a depolarizing agent, whereas the benzylisoquinolinium atracurium (four chiral centres; circled) and the aminosteroid rocuronium are both non-depolarizing drugs. Note the bulky structure of rocuronium in contrast to the slim long chains in suxamethonium and atracurium rendering the last two drugs more vulnerable to plasma breakdown

Figure 1

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