REVIEW ARTICLE

ADVANCES IN NEUROMUSCULAR BLOCKING AGENTS AND REVERSAL AGENTS

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Abstract: *Neuromuscular blocking agents (NMBA) are the integral part of modern anaesthesia. It is used in both operation theatre and intensive care units, facilitating tracheal intubation, optimizing surgical conditions and aiding mechanical ventilation. The advent of newer generation NMBAs including Rocuronium, emerging ultra-short acting Gantacurium and CW002 promise rapid onset with spontaneous recovery and minimal cardiovascular effects. Novel reversal drugs like Calabadion and cysteine – based compounds are under development which aims for broader and faster antagonism of neuromuscular block. The advancement in these drugs would represent more safer, predictable perioperative neuromuscular management*.

Keywords: Neuromuscular blocking agents, Reversal agents, Gantacurium, CW002

Recent advancements in anaesthesia gives us knowledge about neuromuscular blocking agents (NMBAs), which cause muscle relaxation in addition to traditional narcosis and analgesia. This article highlights the indications, mechanism of action, administration methods, adverse effects, contraindications, monitoring, and toxicity of NMBAs, equipping healthcare professionals with the knowledge necessary for optimizing treatment through anaesthesia and other therapeutic

combinations. A clear understanding of NMBAs facilitates precise dosage adjustments and minimizes potential adverse reactions, contributing to safer, more effective patient care.

HISTORY

Harold Griffith and Enid Johnson published their famous paper on the use of curare in general anaesthesia. They administered curare to a young patient undergoing an appendectomy at the Homeopathic Hospital in Montreal.[1] This is considered the first major step towards using NMBA for muscle relaxation during anesthesia. The introduction of curare allowed adequate muscle relaxation at a lighter depth of general anaesthesia, yet well tolerated. Several new compounds were developed and used in clinical practice till date to maintain neuromuscular blockade.

FDA-APPROVED INDICATIONS

Indications for NMBA administration include [2]:

- Endotracheal intubation
- Therapeutic hypothermia after cardiac arrest
- Acute respiratory distress syndrome
- Elevated intraabdominal pressure
- Elevated intracranial pressure
- Status asthmaticus
- Prevention of patient-ventilator asynchrony in patients on mechanical ventilation
- Muscular relaxation for a surgical procedure
- Adjunct therapy for patients undergoing electroconvulsive therapy

MECHANISM OF ACTION

NMBAs act at the neuromuscular junction (NMJ), which consists of 3 parts [2]:

- Presynaptic nerve terminal
- Synaptic cleft
- Postsynaptic nicotinic receptors

Neuromuscular blocking agents (NMBA) are the compounds that act on acetylcholine receptors (Ach R) present at the neuromuscular junction to produce skeletal muscle paralysis without any effects on cardiac and smooth muscle. At the NMJ, motor neuron activity triggers the release of acetylcholine (ACh), which binds nicotinic acetylcholine receptors (nAChRs) densely expressed in the "motor endplate" area of muscle fibers. The nAChRs, pentameric ligand-gated ion channels, open to allow Na+ influx and depolarization when two ACh molecules are bound, thereby initiating muscle action potentials. Rapid breakdown of ACh by acetylcholinesterase ensures brief and controlled contraction. This molecular choreography underlies the clinical power and risk of neuromuscular blocking agents (NMBAs) and the critical importance of controlled blockade and reliable reversal.

Depolarizing Neuromuscular Blocking Agents: -

Depolarizing NMBAs (e.g., succinylcholine) act on receptors at the motor endplate of the neuromuscular junction (NMJ), causing depolarization of the membrane inducing a refractory period. These drugs have an onset of action of 1 minute and a duration of 6 minutes and are rapidly metabolized by plasma butyrylcholinesterase.[3] The continued disruption of ACh-mediated effects causes muscular fasciculation and twitching. Succinylcholine, or suxamethonium, is the only depolarizing NMBA used clinically.

Nondepolarizing Neuromuscular Blocking Agents: -

Nondepolarizing NMDAs prevent acetylcholine from binding to the motor plate at the NMJ by competing for the ACh binding site on the α subunit of nicotinic receptors. As the concentration of non-depolarizing NMBAs at the junction increases relative to ACh, a neuromuscular blockade becomes established.[4]

Ideal NMBAs should have properties like: rapid onset, provide adequate relaxation, predictable duration of action, minimal side effects and easily reversible.[5]

Classification and Pharmacology of Neuromuscular Blockers

Structural and Functional Classes

NMBAs are classified as:

Depolarizing: Succinylcholine, which mimics ACh, causes persistent depolarization, and is rapidly hydrolyzed by plasma cholinesterase for a brief, intense block.

Nondepolarizing: Subdivided into aminosteroidal (rocuronium, vecuronium, pancuronium) and benzylisoquinolinium (atracurium, cisatracurium, mivacurium) agents.

Pharmacokinetics/Dynamics and Clinical Profiles

- Aminosteroidal agents (rocuronium, vecuronium):
    - Metabolized renally/hepatically.
    - Rapid to intermediate onset, with duration adjustable by dose.
    - Minimal histamine release and cardiovascular effects but can accumulate in renal or hepatic failure.

- Benzylisoquinolinium agents (atracurium, cisatracurium):
    - Undergo Hofmann elimination or ester hydrolysis, independent of organ function.
    - Lower risk of accumulation in critical illness or organ dysfunction.
    - Atracurium can cause histamine release; cisatracurium is much less likely to do so.

But search for the ideal NMBA is still on as use of Succinylcholine, though met most of the criteria, is not without side effects that can be ignored. One important area of research is the development of a short-acting non-depolarizing neuromuscular blocking agent with a fast onset & short duration of action, not dependent of end-organ metabolism and rapid & complete reversal.

Recent drug development led to a new series of neuromuscular compounds, called the chlorofumarates such as Gantacurium, CW002, and CW011.[6]

GANTACURIUM

Gantacurium is an asymmetric enantiomeric isoquinolinium diester of chlorofumaric acid. It is available as a lyophylized powder as it is unstable in aqueous solution and reconstitution is required before administration. In amorphous state it is stable for up to 4 weeks at 25-40° C. [7] Gantacurium is an ultra-short acting non-depolarizing NMBA with a rapid onset and a wide safety margin. In human volunteers, the calculated ED_{95} of Gantacurium is 0.19 mg/kg [8] with onset of action less than 3 min and shortened to approximately 1.5 min by increasing the dose to 4× ED_{95}. At these doses, the duration of action of Gantacurium (recovery to train-of-four of ≥ 0.90) approximately 15 min.

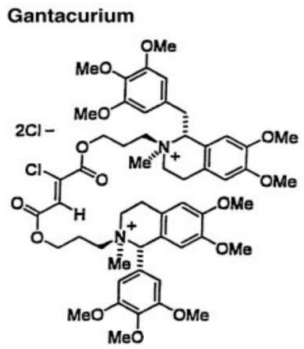

FIG 1: Chemical structure of Gantacurium

Transient(<5min) cardiovascular side effects (Hypotension, Tachycardia) were observed at doses of 3×ED_{95} or higher. Furthermore, humans showed significant histamine release when Gantacurium was administered in doses of 4× ED_{95}. [8] However, at lower doses (2.5× ED_{95}), there was no evidence of histamine release. In animals, no changes in peak inspiratory pressure were observed signifying no muscarinic receptors mediated smooth muscle constriction.

Metabolism of Gantacurium is by chemical degradation through cysteine adduction (fast process) and pH-sensitive hydrolysis (slow process). Cysteine adduction results in replacement of chlorine by cysteine forming a heterocyclic ring which lacks neuromuscular blocking property, can no longer interact with the postjunctional acetylcholine receptor. The elimination of Gantacurium is not renal and hepatic dependent.

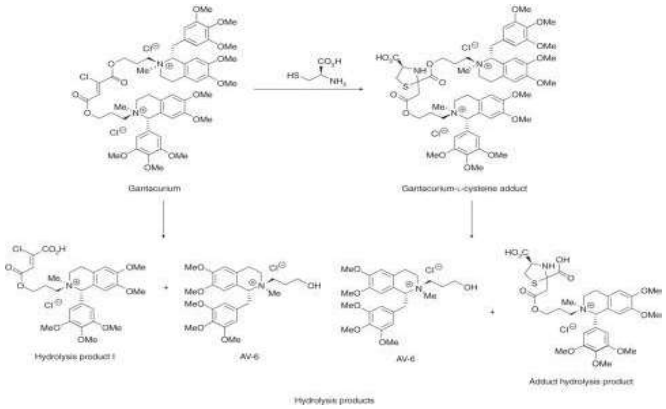

FIG 2: Metabolism of Gantacurium

As Gantacurium is a non-depolarizing NMBA so it can be reversed with cholinesterase inhibitors. Spontaneous recovery time is around 5.7 min without any reversal agent, so the most suitable drug for reversal is Edrophonium(0.5mg/kg), whose peak effect is in less than 2 min. In humans, edrophonium was able to decrease the reversal time of a Gantacurium-induced neuromuscular block at 10% recovery of T1 to a train-of-four ratio ≥ 0.90 to 3.8 min.

Gantacurium is, due to its unique metabolism, rapidly inactivated by cysteine adduction and alkaline hydrolysis. Therefore, Gantacurium can also be reversed by administration of L-Cysteine, commonly administered in humans as an essential component of parenteral nutrition. In animal study L-Cysteine given as a bolus dose of 10–50 mg/kg to reverse neuromuscular

block didn't cause any toxicity, yet clinical studies are still needed for further investigations.

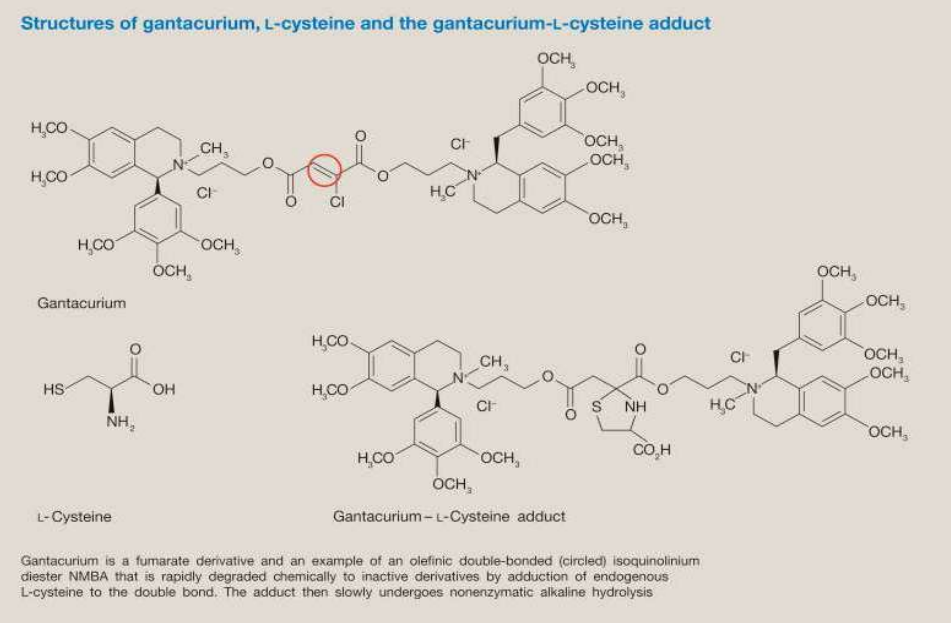

FIG 3: Structure of Gantacurium, L-Cysteine

CW002

CW002 is a new benzoquinolinium fumarate diester non-depolarizing NMBA, which belongs to the family of tetrahydroisoquinolinium compound. The molecular structure of CW002 has similarity with Gantacurium; the difference is that CW002 lacks a chlorine at the fumarate double bond and it is symmetrical unlike Gantacurium.

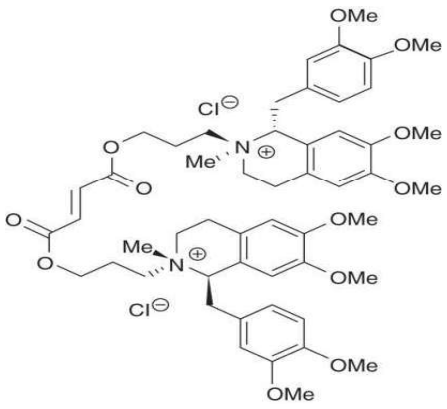

FIG: 4: The chemical structure of CW002

CW002 is also metabolised by endogenous L-Cysteine adduction and alkaline hydrolysis but unlike Gantacurium, cysteine adduction process is relatively slower in case of CW002, making it an intermediate-acting NMBA. The metabolites of CW002 have no clinically significant neuromuscular blocking property (0.01-0.001 times of CW002).

Human study with CW002 revealed its less potency in human than animals. The ED_{95} of CW002 in humans is 0.077 mg/kg. [9]

With a dose of 1.8× ED_{95} (0.14 mg/kg), the block onset time is approximately 90 seconds and the clinical duration is almost 33.8 min (range 28.8–36.1 min). Time from 25 to 75% recovery of T1 is 14 min whereas the spontaneous recovery to a train-of-four (TOF) ≥ 0.90 was 73 min.

CW002 with doses up to 0.14 mg/kg (1.8×ED_{95}) did not result in significant cardiopulmonary side effects or any signs of histamine release so far in limited human study. [9]

As CW002 is a nondepolarizing NMBA, so blockade can be reversed with cholinesterase inhibitors (Neostigmine at a dose of 50mcg/kg, is most suitable), but it only shortened the recovery time minimally. Whereas cysteine adduction to reverse the block in animals showed promising result, human study is yet to be done.

CW011

CW011 is a new asymmetrical benzoquinolinium maleate diester, like CW002 (a symmetrical fumarate), a non-halogenated olefinic diester analogue of Gantacurium.

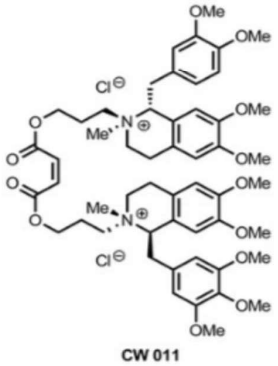

FIG 5: Chemical structure of CW 011 [10]

Animal study showed that CW011 has predictable slower L-Cysteine adduction, making its duration of action longer than that of Gantacurium.[10]

In animals calculated ED_{95} is 0.025 mg/kg (Potency is higher than Gantacurium) and duration of block at 4–5× ED_{95} is approximately 20.8 min (three times longer than that of Gantacurium).

Reversal of neuromuscular block can be achieved by both Cholinesterase inhibitors (Neostigmine) as well as exogenously administered L-Cysteine. L-Cysteine reversal showed full reversal from a neuromuscular block induced by CW011 5× ED_{95} within 2–3 min, proving its superiority over cholinesterase inhibitors in terms of speed and effectiveness of reversal.[10] Human studies are required to investigate and confirm the above-mentioned results in animals.

Reversal of Neuromuscular Block: Mechanisms and Modalities

Ideal characteristics of a reversal agent to antagonise neuromuscular block.[11]

- Can be used to reverse any neuromuscular blocking drug.
- Can be used to reverse any depth of neuromuscular block.
- A rapid onset of maximal effect (within a few minutes).
- No adverse cardiovascular effects.

- No adverse muscarinic effects (e.g. bradycardia, bronchospasm, abdominal pain, nausea and vomiting).
- No histamine release or risk of anaphylaxis.
- Not dependent on organ elimination.
- No ceiling effect.
- Does not produce depolarising block if given in excess.
- Low cost.

Conventional Reversal: Anticholinesterases

Neostigmine inhibits acetylcholinesterase, extending ACh half-life, and enabling competition with nondepolarizing agents. Yet, it has a "ceiling effect"—cannot reverse deep blockade (TOF count <2), and is associated with cholinergic side effects (bradycardia, bronchorrhea), requiring co-administration of antimuscarinics. Meta-analyses show unreliable reversal with neostigmine in deep blockades and high residual paralysis rates (up to 32% after moderate block, >95% after deep block within 60 min).

Sugammadex: A Selective Relaxant Binding Agent

Mechanism: Sugammadex, a modified γ-cyclodextrin, encapsulates aminosteroidal NMBAs in a 1:1 host-guest complex, rapidly reducing unbound drug concentration and driving gradient-mediated removal from the NMJ. [11]

Recovery to TOFR >0.9 occurs within 1–3 min even after deep block, without muscarinic side effects. Sugammadex does not require coadministration of an antimuscarinic agent. Sugammadex has a lipophilic core and eight outer tails with a negative charge at their tips (FIG 6). These negative charges attract the positively charged quaternary ammonium group on the aminosteroid molecule, drawing the neuromuscular blocking drug into the more lipophilic core of the toroid and holding it there irreversibly. The attraction of sugammadex for rocuronium is as strong as the attraction of acetylcholine to the postsynaptic nicotinic receptor.

The rocuronium–sugammadex complex is excreted in the urine with a plasma clearance similar to the glomerular filtration rate.

Comparative Clinical Data:

Multiple systematic reviews and meta-analyses found that Sugammadex produces more reliable, faster, and complete recovery than neostigmine, with a significant reduction in residual blockade and airway complications. rNMB incidence post-sugammadex: 2.8% at 6 min, <1% by 15 min. For neostigmine: 82% at 6 min, 14–32% at 10–60 min.

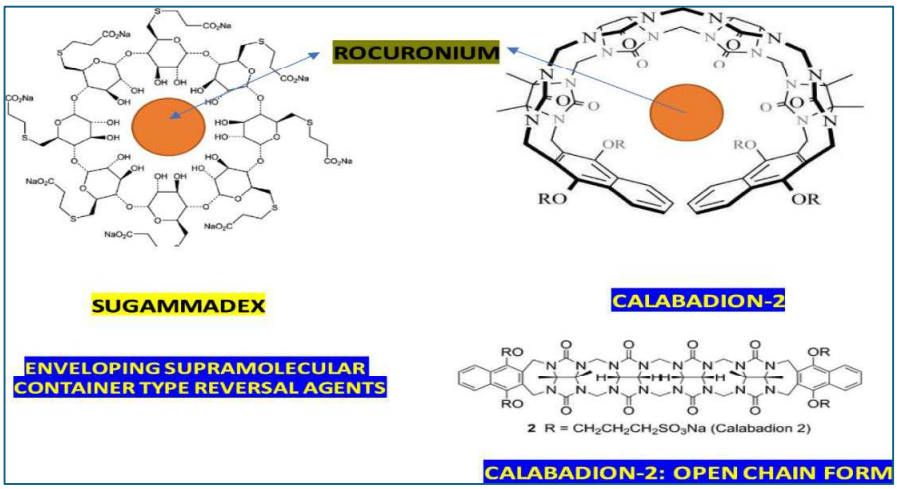

Fig 6: Structures of neuromuscular reversal agents

Agent	Reversal Time (TOFR ≥0.9)	Reversible NMBAs	Safety Profile	Special Notes
Sugammadex	1–3 minutes	Rocuronium, Vecuronium	Rare anaphylaxis	Not for benzylisoquinoliniums
Calabadion-2	<1 minute (preclinical)	Steroidal + benzylisoquinoliniums	High biocompatibility	Not yet available clinically
Adamgammadex	2.9–3 minutes	Rocuronium	Good tolerance	Comparable or superior to sugammadex
Neostigmine	7–10 minutes	Most non-depolarizing agents	Muscarinic side effects	Requires T2 return; antimuscarinic needed

Table 1: Comparative list of neuromuscular agent reversals.

Macrocyclic and Supramolecular Advances

Calabadion

Calabadion-1: Acyclic cucurbituril analog with fast reversal of both steroidal and benzylisoquinolinium NMBAs in rats. Time to TOFR >0.9: 84s for rocuronium, much shorter than neostigmine (4.6 min) and placebo (16.2 min). Binding constants similar to sugammadex for rocuronium; weaker for Cisatracurium.[12]

Calabadion-2: Second-generation with “naphthalene walls” and 89-fold increased affinity for rocuronium (Ka 3.4 × 10^9 M^-1), dose-dependent and faster reversal of all major nondepolarizing agents in animal studies. 49–62% renal excretion within one hour and high selectivity (18,900 times preference for rocuronium over Ach). Demonstrated to reverse deep blocks with “broad spectrum” efficacy in preclinical models, outperforming sugammadex in affinity and recovery times.[12]

Pillararenes

Sulfonated Pillararene (SPA): Experimental studies showed rapid in vivo reversal of succinylcholine-induced block with strong host–guest interactions and mitigation of hyperkalemia, arrhythmias, and rhabdomyolysis. High binding affinity (10^5 M^-1) and clinical promise for depolarizing block reversal, a unique advance not achieved with cyclodextrins or calabadion.[13]

Mechanism of reversal

Pillararenes, particularly those with sulfated modifications like Pillar MaxQ (P6AS), demonstrate high binding affinities for specific NMBAs, especially those with quaternary ammonium groups, such as rocuronium and vecuronium. [14]

By encapsulating these NMBAs within their cavity, pillararenes effectively sequester them, reducing their concentration at the neuromuscular junction and allowing acetylcholine (ACh) to bind to its receptors, thereby reversing the blockade and facilitating the return of muscle function.

Studies have shown that P6AS binds to rocuronium and vecuronium with affinities significantly higher than that of sugammadex, a clinically used NMBA reversal agents. [15]

Advantages over existing reversal agents

- Higher Potency yet Reduced Side Effects
- Potential for Broader Spectrum: Pillararenes may hold potential for reversing the effects of a wider range of NMBAs, and could offer an alternative for patients who may not tolerate existing reversal agents.
- Decrease in postoperative pulmonary complications (hypoxemia, atelectasis, pneumonia)
- Lower rates of airway obstruction and reintubation
- Reduced PACU and hospital stay and Increased patient satisfaction.

Conclusion: A New Era of Individualized Neuromuscular Blockade

The advent of designer reversal agents (sugammadex, calabadion, pillararenes), coupled with quantitative monitoring, offers near-total precision in the induction and termination of neuromuscular blockade. While challenges remain—especially validation beyond animal models and translation to special populations—the broad-spectrum reversal, speed, safety, and selectivity of these agents herald a transformation in perioperative care. Continued research, adherence to international guidelines, and investment in robust monitoring will be critical for this new paradigm to realize its full patient safety potential.

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