Editorial

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Neuromuscular Blocking Drugs: Where are We Now?

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Introduction of neuromuscular blocking drugs (commonly though incorrectly called muscle relaxants) has revolutionized the modern anesthetic practice. They are usually used as an adjunct to anesthesia for attaining skeletal muscle paralysis to facilitate tracheal intubation and to optimize the surgical field. Facility and expertise to support respiration and mechanical ventilation should be available before using these drugs. As they do not produce sedation, amnesia or analgesia, general anesthesia with additional analgesia and amnesia are required for preventing awareness during the procedure. In the Intensive Care Unit (ICU), they are used to facilitate mechanical ventilation and minimize patient-ventilator asynchrony. They also reduce the oxygen consumption and help to reduce raised intracranial tension.

Neuromuscular blockers bind to the postsynaptic acetylcholine receptors blocking neuromuscular transmission causing skeletal muscle paralysis. These drugs are classified as depolarizing and nondepolarizing agents, according to their mechanism of action. Depolarizing agents bind to the acetylcholine receptors causing persistent depolarization producing muscle fasciculations followed by flaccid paralysis. Succinylcholine is the only currently used depolarizing agent. Nondepolarizing agents act as competitive antagonists of the nicotinic receptors, blocking the action of acetylcholine causing skeletal muscleparalysis. Commonly used non depolarizing drugs are of two groups, aminosteroids (pancuronium, vecuronium, rocuronium) and benzylisoquinoliniums (atracurium, cisatracurium, doxacurium, mivacurium).

'Curare" was the name used to describe the poisonous extract obtained from woody wines of South America. This has been traditionally used to make poison tipped arrows for hunting animals which die due to respiratory paralysis and suffocation. Natives called this plant "woorari", which became "curare" to the Europeans. In 1825, Sir Benjamin Brody found that curare does not kill the animal, if its respiration is supported artificially. He also suggested that curare could be used for the treatment of tetanus. Waterton in 1859 tried it for treating hydrophobia, but the patient died before the drug was administered. George Harley in 1850 showed that curare was effective in the treatment of tetanus and strychnine poisoning.

It was Claude Bernard in 1857 who demonstrated that the effect of curare is due to the blockade of nerve impulses across the neuromuscular junction. In 1942, Wintersteiner and Dutcher isolated the alkaloid d-tubocurarine from the plant Chondrodendron tomentosum [1]. The first clinical use of curare was probably in 1940 when A.E. Bennett, a psychiatrist, combined metrazol injections with curare to neutralize the strong muscle contractions of convulsive shock therapy [2].

On 23rd January 1942, Harold Griffith, anaesthetist from Montreal used curare for the first time in anaesthesia for a patient undergoing appendicectomy [3]. This was introduced into anaesthetic practice in the 1940s for tracheal intubation and skeletal muscle relaxation for abdominal surgeries. However, its potential for histamine release and hypotension was a major drawback.

Pal in 1899 had shown that physostigmine could reverse the block produced by curare [4]. From the time of initial use of tubocurarine in clinical anaesthesia, anticholinesterase drugs neostigmine and pyridostigmine has been used for restoring the neuromuscular blockade.

In 1947, Daniele Bovet, a Swiss-Italian pharmacologist introduced the first synthetic clinically used neuromuscular blocking drug, gallamine, which was a non depolarising agent, the action of which was reversible with anticholinesterases similar to tubocurarine. It is currently out of use due to its vagolytic action causing

tachycardia and hypertension. It has the potential for histamine release and anaphylactoid reaction has been reported with its use. As gallamine can cross the placenta, it is best avoided in obstetric practice.

Decamethonium was the first synthetic depolarizing neuromuscular blocking agent discovered by Paton in 1949 [5]. It was different from d-tubocurarine in that the duration of action was shorter with fasiculations preceding the block and the action was not reversed with anticholinesterases.

Bovet in 1949 published the work on succinylcholine a synthetic depolarizing agent, with a structure of two acetylcholine molecules for which he was awarded Nobel Prize in 1957. The rapid onset of its action producing flaccid paralysis and short duration of action due to its rapid metabolism by plasma cholinesterase made it attractive for tracheal intubation, especially for rapid sequence induction-intubation (RSI). However, its undesirable effects like cardiac dysrrhythmias including sinus arrest, potential for hyperkalemia and malignant hyperpyrexia, rise in intracranial, intraocular and intragastric pressures and postoperative muscle pain probably due to the muscle fasiculations made it an undesirable choice in many situations. As most of these were due to the result of depolarizing block, search began for a nondepolarizing agent having an onset, quality and duration of action comparable to that of succinylcholine.

In 1964, Hewett and Savage synthesized an aminosteroidal molecule with two quaternary ammonium groups which had curare like effects, and named pancuronium, which replaced the other non depolarising neuromuscular blockers due to its relative safety profile [6]. The vagolytic effect and prolonged action of pancuronium initiated the search for compounds devoid of these unwanted effects.

Savarese and Kitz in 1975 defined ideal non depolarising neuromuscular blocking agent as one with brief, non cumulative, action with rapid onset and recovery which is reversible by antagonist and lackingserious side effects [7].Thus came up the introduction of the aminosteroidal drug vecuronium which almost met the criteria. However, its prolonged action in those with hepatic and renal failure was a serious drawback.

Pipecuronium, an analogue of vecuronium is a very potent bisquaternary aminosteroid neuromuscular blocking agent with a much prolonged duration of action recommended only for lengthy surgical procedures.The duration of action is further prolonged in patients with renal impairment.

In 1973 Stenlake and colleagues synthesized atracurium, a benzylisoquinoline molecule causing non depolarizing block with an intermediate duration of action which was not affected by renal or hepatic failure as it undergoes Hofmann elimination, a nonenzymatic degradation under physiological pH and temperature. But its potency for histamine release and hypotension was a serious drawback [8]. Laudanosine, a metabolite of atracurium, has central nervous system stimulating effects which could result in seizures. However, Cis-atracurium, an isomer of atracurium, wasfound to befour times potent than atracurium and does not release histamine, but 77% of its elimination is organ-dependant, which was a serious disadvantage.

The continued search for better nondepolarizing agents led to the synthesis of benzylisoquinolinedrugs like mivacurium and doxacurium in the early 1980s. Mivacurium is an ester-linked compound metabolized by plasma cholinesterase, having a slower onset than succinylcholine, but had a rapid recovery [9]. Doxacurium had the advantage of a better cardiovascular profile over mivacurium, but became unpopular due to its longer duration of action.

Bowman in 1988 established that with the aminosteroids the speed of onset is related to the potency, with less potent drugs having a faster onset of action [10]. Rocuronium an analogue of vecuronium was found to have an onset comparable to that of succinylcholine emerged as a substitute for it especially for RSI due its lack of the side effects of depolarizing drugs. However, the longer duration of action with kidney and liver dependant elimination turned out to be its disadvantages [11]. Sugammadex, a selective binding agent encapsulates rocuronium making it inactive in the plasma and unable to bind to the acetylcholine receptor at the neuromuscular junction reversing the blockade within minutes [12]. Rocuronium–sugammadex complex is eliminated through kidney. There have been reports of anaphylaxis or anaphylactoid reactions to sugammadex which prevents its routine usage for reversal.

Rapacuronium is another analogue of vecuronium introduced in 1990 with a rapid onset close to that of succinylcholine, but was withdrawn due to instances of severe bronchospasm [13].

All the currently available neuromuscular blocking drugs have their limitations for clinical use. The searchstill continues for an ideal nondepolarizing agent having a rapid onset, easily reversible, non-cumulative action, non organ dependent elimination, free from hemodynamic side-effects having no

pharmacologically active metabolites [14]. However, the rapid onset, quality of relaxation and speedy recovery of the depolarizing agent succinylcholine is unique despite its undesirable effects and its use will continue till the search for an ideal non-depolarizing agent to replace it is succeeded.

Gantacurium is a new experimental non depolarizing neuromuscular blocking drug representing the third generation of tetrahydroisoquinolinium compound [15]. It has a rapid onset and an ultrashort duration of action to challenge the pharmacological profile of the gold-standard ultrashort acting depolarizing agent succinylcholine. It undergoes rapid "chemo-inactivation" by cysteine adduct formation independent of body pH and temperature followed by biodegradation via ester hydrolysis and the by-products eliminated throughkidney and liver.Recovery from gantacuriuminduced neuromuscular blockade can be shortened by administration of l-cysteine [16]. Introduction of this novel non depolarizing neuromuscular blocker into clinical practice would probably replace the depolarizing drug succinylcholine

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