Azasteroids as Promising Neuromuscular Blockers: A Review

Prafulla M Sabale, Prashant Prajapati, Pratik G Kalal, Drishti B Nagar
Department of Pharmaceutical Chemistry, Parul Institute of Pharmacy, Limda-391 760, Vadodara, Gujarat, India.

ARTICLE INFO
Article history:
Received on: 15/10/2012
Revised on: 28/10/2012
Accepted on: 04/10/2012
Available online: 30/11/2012

Key words:
Neuromuscular blockers, Quaternary ammonium muscle relaxants, depolarizing neuromuscular blockers, Non-depolarizing Neuromuscular blockers, Bisquaternary azasteroids.

ABSTRACT
Neuromuscular blockers are used during surgery with anesthesia to cause relaxation of muscles and control muscle movements. The purpose of this review is to focus on the synthesis and pharmacological activity of the neuromuscular blockers, to compare the main differences between the available polarizing and non-depolarizing neuromuscular blockers. Continuous improvement of knowledge about neuromuscular blockers in respect to synthesis, their pharmacology, adverse effects, and toxic effects were unanswered questions about neuromuscular junction and neuromuscular blockade in children is essential for the correct use of these drugs. In this review article, structure-activity relationships within polarizing and non-depolarizing neuromuscular blockers have been reviewed.

INTRODUCTION
This review article deals with a comprehensive survey of the progress in chemical, pharmacological, and some respects of clinical studies of neuromuscular blocking agents used in clinical practice and under development, including the synthesis, structure elucidation pharmacological actions and structure activity relationship of steroidal and non-steroidal derivatives. Quaternary ammonium muscle relaxants are quaternary ammonium salts used as drugs for muscle relaxation, most commonly in anesthesia. It is necessary to prevent spontaneous movement of muscle during surgical operations. Muscle relaxants inhibit neuron transmission to muscle by blocking the nicotinic acetylcholine receptor. What they have in common, and is necessary for their effect, is the structural presence of quaternary ammonium groups, usually two. Some of them are found in nature and others are synthesized molecules (Raghavendra, 2002; Bowman, 2002). Curare is a crude extract from South American plants. It was known in the 19th century to have a paralysing effect. d-tubocurarine a mono-quaternary alkaloid was isolated from Chondodendron tomentosum in 1942, and it was shown to be the active chemical in curare that had the paralysing effect. At that time it was known that curare and therefore d-tubocurarine worked at the neuromuscular junction. The isolation of tubocurarine and its marketing as the drug Intocostrin led to more research in the field of neuromuscular blocking drugs. Scientists figured out that the potency of tubocurarine was related to the separation distance between the two quaternary ammonium heads (Raghavendra, 2002; Nedegard, 2003).

Further research led to the development of synthesized molecules with different curariform effects, depending on the distance between the quaternary ammonium groups. One of the synthesized bis-quaternaries was decamethonium a 10-carbon bis-quaternary compound. Following research with decamethonium, scientists developed suxamethonium, which is a double acetylcholine molecule that was connected at the acetyl end. The discovery and development of suxamethonium lead to a Nobel Prize in medicine in 1957. Suxamethonium showed different blocking effect in that its effect was achieved more quickly and augmented a response in the muscle before block.
Also, tubocurarine effects were known to be reversible by acetylcholinesterase inhibitors, whereas decamethonium and suxamethonium blockers were not reversible (Raghavendra, 2002; Bowman, 2002).

Another compound malouétine that was a bis-quaternary steroid was isolated from the plant *Malouetia bequaertiana* and showed curariform activity. This led to the synthetic drug pancuronium a bis-quaternary steroid and subsequently other chemicals that had better pharmacological properties as drugs (McKenzie, 2000).

### Classification of Neuromuscular blockers

Most widely neuromuscular blockers are classified into two classes: depolarizing and non-depolarizing neuromuscular blockers (Joao et al., 2000).

- **Depolarizing neuromuscular blockers:** There is only one depolarizing agent, succinylcholine, which mimics Ach but stays at the neuromuscular junction for a longer period of time. At first, succinylcholine stimulates the muscles, causing transient twitching and can cause painful fasciculation.

- **Non-depolarizing neuromuscular blockers:** They act by blocking the binding of Ach to the receptor. All of the agents except succinylcholine are non-depolarizing, which means that they work by binding to the Ach receptors on the muscle side of the junction. With these receptors blocked, Ach cannot transmit the nerve impulse, so the muscle cannot depolarize and contract.

### Neuromuscular blockers

are also classified on the basis of the chemical structure:

#### Succinylcholine and Decamethonium

Succinylcholine (2) was synthesized by connecting two acetylcholine (1) molecules and has the same number of heavy atoms between methonium heads as decamethonium (3). Just like acetylcholine, succinylcholine, decamethonium and other polymethylene chains, of the appropriate length and with two methonium, heads have small trimethyl onium heads and flexible links. They all exhibit a depolarizing block (Katz et al., 1966).

#### Tetrahydroisoquinoline Derivatives

Compounds based on the tetrahydroisoquinoline moiety such as *Atracurium* (4), mivacurium (Basta, 1992) (5) and doxacurium (Basta et al., 1988) (6) would fall in this category. They have a long and flexible chain between the onium heads, except for the double bond of mivacurium. D-tubocurarine and dimethyltubocurarine are also in this category. Most of the agents in this category would be classified as non-depolarizing.
A neuromuscular non-depolarizing agent is a form of neuromuscular blocker which do not depolarize the motor end plate. The quaternary ammonium muscle relaxants belong to this class. Below are some of the more common agents that act as competitive antagonists against acetylcholine at the site of postsynaptic acetylcholine receptors. Tubocurarine (7), found in curare of the South American plant Pareira, Chonodendron tomentosum, is the prototypical non-depolarizing neuromuscular blocker. It has a slow onset (>5 min) and a long duration of action (1–2 hours). Side effects include hypotension, which is partially explained by its effect of increasing histamine release, a vasodilator (Inada et al., 1986) as well as its effect of blocking autonomic ganglia.

Gallamine and Other Chemical Classes

Gallamine (Ostergaard et al., 1989) (8) is a trisquaternary ether with three ethonium heads attached to a phenyl ring through an ether linkage. Many other different structures have been used for their muscle relaxant effect such as stercuronium iodide.
Aminosteroids

Pancuronium (Bowman et al., 1988; Norman et al., 1971) (10), vecuronium (Bowman et al., 1988; Foldes et al., 1983) (11), rapacuronium (Bevan, 2000) (12), rocuronium (England et al., 1996) (13), malouetine (Janot et al., 1960, Quevauviller et al., 1960) (14), dipyramid (William et al., 1964) (15), pipecuronium (Denman et al., 1996; Diefenbach et al., 1993) (16), chandonium (Singh et al., 1974; Gandhia et al., 1974) (17), and other bisquaternary ammonium compounds are aminosteroidal agents.

These agents constitute the majority of the clinically-relevant neuromuscular blockers. They act by competitively blocking the binding of Ach to its receptors, and in some cases, they also directly block the ionotropic activity of the Ach receptors (Bufler et al., 1996).

\[
\text{Ach} + \text{Me}
\]

\[
\text{Me}
\]
Aminosteroids are Non-depolarizing neuromuscular blockers having a common the steroidal structure with quaternary nitrogen which provides a rigid and bulky body (Lee, 2001).

Due to flexibility in steroidal molecule various researchers synthesized aminosteroids with promising neuromuscular blocking activity will be discussed separately. The neuromuscular blocking agents available are nonsteroidal and azasteroidal. Advances in both these areas have been reviewed (Rang, 2003; Singh et al., 1984; Booij et al., 1984; Singh et al., 1979; Buckett, 1972; Buckett, 1975). The work on azasteroidal neuromuscular blocking agents has been reviewed by different workers. The findings of the work are discussed here;

Janot et al, synthesized steroidal alkaloid malouetine (Janot et al., 1960) (14) and its C-3 and C-20 configurational isomers (Alauddin et al., 1962; Strange et al., 1970). Due to free rotation of the side chain, and as such study of bisonium azasteroids having both the quarternary ammonium groups directly attached to the nucleus was considered worthwhile.

Alauddin et al, synthesized a series of 3α,17α-bis(quarternary ammonium)-5α-androstanes (Alauddin et al., 1965) (18), in which the interonium distance (0.92-1.06nm) was near the favourable range and steric hindrance to post junctional binding by β- face angular methyl groups on C-10 and C-13 was excluded. These compounds showed pharmacological activity, though less than that of (+)-tubocurarine.

Davis et al reviewed on dipyridium chloride (William et al., 1964; Rosemarie et al., 1964) (15) and its eight isomers (Bamford et al., 1967; Davis et al., 1967) which involved in vivo test on cat and monkey sciatic nerve tibialis muscle preparation it was found that 3β- isomers were in general more potent than the corresponding 3α- compounds and there was no general relationship between potency and interonium distances.

Clarke et al at Glaxo Laboratories (UK) showed quarternary salts (Busfield et al., 1968) (19) derived from alkaloid derivatives. The bisquaternary compounds reported possess the interonium distance of 1.01nm. Seven of the eight 3- monoquaternary compounds tested were also potent neuromuscular blocking agents; this observation may not be taken as a convincing evidence for the one point attachment, since the second nitrogen could get protonated in the system and thus provide second cationic head. N, N- dimethylconessine (4; R1 = H, R2 = Me) had potency comparable to that of (+)-tubocurarine; its duration of action was comparable to that of suxamethonium in the cat. The rate of recovery was slower in monkey and man (Verner, 1968). The related drug stercuronium iodide (20) is a monooquaternary compound. Wieriks et al reported non-depolarizing type, has no histamine release property and has the duration of action lying between those of gallamine and suxamethonium (Hespe et al., 1971).

Pancuronium bromide (Pavulon®) (Baird et al., 1967; McDowell et al., 1969; Dick et al., 1970) (10) is a successful drug discovered at the Organon Laboratories Limited (UK). Rapacurionium (12) and rocuronium (13) are pancuronium analogues.

Buckett et a (Speight et al., 1972; Buckett et al., 1973, Savage et al., 1968, Lewis et al., 1967 ) study on 2β-amino-3α-hydroxyl-5α-androstanes and derivatives and the corresponding 3α- amino-2β- hydroxyl isomers. A substitute in specific molecular conformation akin to the neurotransmitter acetylcholine (1) and thus most potent of series 3α-acetoxy-2β-piperidino-5α-androstan-17-one-methyl bromide (21) may be expected to occupy the transmitter of action and neuromuscular transmission. As the monoquaternary analogue (21) had only a low activity, it was thought that a bisquaternary azasteroid may be potent and pancuronium bromide (10) was ultimately synthesized (Buckett et
al., 1973) and tested. Even here the 16- and 17- substituents are pseudoequatorial.

A notable discovery after pancuronium from the Organon Laboratories, is one of the potent non-depolarizing neuromuscular blocking agent vecuronium bromide (Org NC 45; Nouran) (11) (Buckett et al., 1973; Durant et al., 1983; Durant et al., 1980; Booij et al., 1983), which has short duration and rapid onset of action and little accumulative effect. It is suggested that quarternary ring D acetylcholine fragment is intrinsically suited to skeletal muscle nicotine receptors and is relatively unsuited to cardiac muscarinic receptors.

Pipecuronium bromide (RGH-1106, Asduan) (16) (Tuba, 1980), an analogue of pancuronium (10), was discovered at the laboratories of Gadeon Richer Ltd. (Budapest, Hungary). Pipecuronium is a non-depolarizing blocker and in animal experiments (Karpati et al., 1980; Alyautdin et al., 1980), it has shown activity 2-4 times than that of pancuronium and duration of action is twice as long as that of pancuronium in equiactive doses.

Singh et al, synthesized compound which proved to be of particular interest was 17α-methyl-3β-pyrrolidino-17α-aza-D-homo-5-androstene dimethiodide (Chandonium Iodide) (Singh et al., 1974) (17) (now candocuronium). The X-Ray diffraction studies showed the interonium distance to be 1.029nm (Gandhia et al., 1974). Taking chandonium (17) as a model several structural modifications been carried out. Certain interesting structure activity relationships are evident.

The saturated congener dihydrochandonium iodide (23) and the analogues possessing bulkier cationic heads have been synthesized (Gandhia et al., 1974). Saturation of 5,6- double bond in chandonium and increase in onium bulk in (17) and (24) diminish the potency (Apon et al., 1979). Dihydrochandonium iodide has half the potency of chandonium. It is again short acting but has lesser vagolytic action as noted in anaesthetized cat.

The Gadeon Richter scientists have designed RGH-4201 (25), 3α-isomer of dihydrochandonium (24), and showed it to be equipotent to chandonium in conscious dog, but 2-3 times less active in anaesthetized cat (Biro et al., 1981). Notwithstanding the observation that there is a decrease in potency with increase in the onium bulk in chandonium iodide (17), HS-627 (26), which contains acetylcholine-like moiety was prepared (Foldes et al., 1983) by Singh et al since, pancuronium bromide has bulky...
quaternary groups and contains acetylcholine like fragments HS-627 (26) and HS-626 (27) to be 1.033nm. The synthesis of 19-norchandonium iodide (28) by Organon group has been reported (Singh et al., 1979).

The 19-nor analogue (28) was 3-4 times less active than chandonium iodide (17). Interestingly, the enantiomer (29) (Marshall et al., 1984) has virtually the same potency as (28). It appears that the effect of complete change in steric configuration is insignificant compared to that resulting from the change in lipophilicity caused by the removal of the 10-methyl group of chandonium iodide.

Jindal et al has synthesized new analogue (30) of chandonium and evaluated for neuromuscular blocking activity (Verma et al., 1994; Yadav, 1993).

Yadav et al, synthesized a new azasteroideal neuromuscular blocker having acetylcholine like moiety in ring A, was found to be half as active as chandonium (30). (Yadav et al., 2001) Presence of acetylcholine like moiety in ring A enhances the neuromuscular blocking activity. They have synthesized bisquaternary azasteroid having acetylcholine like moiety at 4th position in ring A while retaining structural features of chandonium iodide. The compound was found to be half as active as chandonium. Jindal et al, reported the design of some quaternary ammonium steroids in pregnane series, which have in part structural features corresponding to HS-467 or chandonium (17) (Abraham et al., 1993).

Among these compounds (31) found to be more potent with free hydroxyl group at position 20.

Jindal et al, in his next research he synthesized 16β-piperidinosteroidal derivatives (Jindal et al., 2001). Among these compounds (34) was found to be more active than d-tubocurarine. Jindal et al, synthesized 16β-N-methylpiperazino steroidal derivatives (Jindal et al., 2002) 16-Acetoxy derivative (36) was found to be more potent than pipecuronium bromide.
Dubey \textit{et al.}, synthesized 16-(2- and 3-pyridylmethylene) dehydroepiandrosterone derivatives (Dubey \textit{et al.}, 2010).

Ranju Bansal \textit{et al.}, synthesised eighteen new quaternary ammonium salts 16E-arylidene androstene derivative as skeletal muscle relaxant (Bansal \textit{et al.}, 2011).

Among this series (41 d) was found to be having rapid onset of action at 1µM concentration in 2 minutes for fifty percent blockade of chick biventer cervicis preparation.
CONCLUSION

In the near future "ideal" short-acting or other side effect–free NMBs may be discovered assuming new promises of Molecular Biology and Genetic sciences will be realized by creating optimally acting new anesthetic agents that will produce skeletal muscle relaxation matching the pharmacokinetic patterns of all anesthesia, analgesia and amnesia components. The anesthesia professional should be aware not only of the latest developments in biomedical sciences related to the profession.

ACKNOWLEDGEMENT

We would like to thanks Dr. Devanshu J Patel, Managing trustee Parul Trust for providing necessary infrastructure and Dr. Rajesh K. S. Principal, Parul Institute of Pharmacy, Limda, Vadodara for offering precious suggestions.

REFERENCES


Yadav MR. Acetylcholine like some potential neuromuscular blockers. Ind J Chem. 1993; 32B: 746-750.


How to cite this article: