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An Examination Of Structure-Activity Relationships And Chemical Nomenclature According To Iupac: The Case Of Steroid-Based Neuromuscular Blocking Agents

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ABSTRACT

Neuromuscular blocking agents comprise a class of drugs that block neuromuscular transmission. Historically used since the 16th century, they originate from natural substances like D-tubocurarine. Modern research has led to the development of synthetic derivatives, particularly steroid-based neuromuscular blocking agents, in order to optimize their pharmacological profile.

Steroid-based neuromuscular blocking agents are complex molecules whose pharmacological properties (activity, metabolism, toxicity) are closely linked to their chemical structure. Despite the complexity of their nomenclature, it is homogeneous because it is based on a common structural core, cyclopentanoperhydrophenanthrene. Understanding the structure-activity relationships has been fundamental to the development of agents with optimized pharmacological profiles. This article addresses the various aspects of the structure-activity relationship of steroid-based neuromuscular blocking agents and focuses on their chemical nomenclature based on the standard terminology of the International Union of Pure and Applied Chemistry (IUPAC).

KEYWORDS: Neuromuscular blocking, structure-activity relationships, nomenclature, IUPAC.

I. INTRODUCTION

Neuromuscular blockade relies on the use of a group of drugs that act specifically at the neuromuscular junction, whose mechanism of action has already been described by several authors [1,2]. Historically, these substances were used by Native Americans as early as the 16th century. The term "curare" was first introduced in 1648 by Margraaf.

Among the natural substances are D-tubocurarine, extracted from the vines of Chondodendron tomentosum [3], toxiferine, derived from Strychnos toxifera [4], and malouetine, extracted from Malouetia bequaertiana [5]. These molecules represent the historical natural models of curare, which now have no therapeutic utility but retain scientific and historical interest.

Subsequently, other neuromuscular blocking agents were developed, notably those belonging to the benzylisoquinoline family [6,7] and those with a steroid nucleus [8,9].

Since 1942, researchers have significantly contributed to the study of structure-activity relationships, aiming to improve the pharmacological properties of these agents, particularly their duration of action and the reduction of toxic effects [10,11]. This research has enabled the development of new derivatives with an optimized pharmaco-toxicological profile [12].

In this perspective, the present work proposes, in its first part, an examination of the structure-activity relationship elements of several steroid-based neuromuscular blocking agents. The second part is devoted to the chemical nomenclature of cyclopentanoperhydrophenanthrene derivatives.

Although the naming of neuromuscular blocking agents is complex and multifaceted, we present here the official chemical nomenclature as established by the International Union of Pure and Applied Chemistry (IUPAC) [13].

II.REVIEW OF THE STRUCTURE-ACTIVITY RELATIONSHIP ELEMENTS IN STEROID-BASED NEUROMUSCULAR BLOCKING AGENTS

II.1 Structure-Activity Relationship Of The Steroid Nucleus

The structural particularity of the steroid nucleus lies in its rigidity and bulkiness, characteristics that are essential for ensuring affinity and selectivity towards the nicotinic acetylcholine receptors at the neuromuscular junction [14,15].

Furthermore, it has been demonstrated that curares with a bulky nucleus (pachycurare) are all non-depolarizing agents [16]. Their action relies primarily on the steric hindrance exerted by the steroid nucleus, which prevents receptor activation.

Moreover, the androstane nucleus is lipophilic in nature. An excessive increase in this lipophility appears to reduce the pharmacological activity of steroid-based neuromuscular blocking agents [17].

II.2 Structure-Activity Relationship Of Mono-And Bis-Quaternary Neuromuscular Blocking Agents

Although these derivatives possess one or two quaternary motifs, which likely correspond to a cyclic acetylcholine molecule, their linkage to the steroid nucleus makes them chemically distinct from acetylcholine, while still maintaining a strong affinity for the nicotinic receptor at the neuromuscular junction.

The ten-carbon atom rule must always be respected: the distance between two onium groups is typically ten atoms. This distance represents an estimate of the space separating the accessible receptor sites of the muscle nicotinic receptor for neuromuscular blocking agents. It corresponds to approximately 20 Å to allow for neuromuscular blockade. A shorter distance, on the other hand, is associated with ganglionic blockade [18].

Regarding the relationship between activity potency and onset of action, these two properties are inversely proportional. This is the case with rocuronium, which has a rapid onset of action but a lower potency than its predecessors, pancuronium and vecuronium [17,19].

Vecuronium (monoquaternary) and pancuronium (biquaternary) possess similar potency, directly linked to the D-ring of the steroid nucleus, to which a cis-pyridinium group (the cyclized form of acetylcholine) is attached [20]. This group binds to the anionic pole of the nicotinic acetylcholine receptor, which explains why the neuromuscular blockade depends little on the degree of ionization of the A-ring of the steroid nucleus.

For bisquaternary neuromuscular blocking agents, it has been demonstrated that the inter-onium distance determines the potency of the neuromuscular blockade and allows them to be distinguished from molecules responsible for ganglionic blockade [21]. This onium head is generally associated with a strategically positioned hydrogen bond acceptor group, which forms a hydrogen bond with the receptor. This interaction helps to improve the potency of monoquaternary neuromuscular blocking agents [22].

As mentioned previously, the lipophilicity of the amino-steroid is inversely proportional to the potency of the neuromuscular blockade. Thus, when a nitrogen-quaternizing group attached at position 16 of the steroid is bulkier than a simple methyl group, the molecule becomes more lipophilic and therefore less potent. The same applies to a 17-acyloxy group that is more bulky than acetoxy.

A radical group bulkier than a methyl group creates steric hindrance, thereby reducing the potency of action. This is what is observed with rocuronium, whose potency is lower than that of vecuronium and pancuronium.

II.3 Structure-Metabolism Relationship

The ester functions, located at positions 3 and 17 of amino-steroid neuromuscular blocking agents, are sensitive to the action of hepatic esterases. They undergo deacylation, leading to the formation of metabolites such as the 3-OH, 17-OH, and/or 3,17-dihydroxy compounds.

In general, these metabolites are less potent than their parent compounds [24]. However, there are exceptions: some metabolic derivatives, particularly the 3-OH and 3,17-diacylated amino-steroids, can retain significant pharmacological activity [23].

II.4 Structure-Toxicity Relationship Of Steroid-Based Neuromuscular Blocking Agents

The occurrence of side effects is closely linked to the potency and the onset of action of neuromuscular blocking agents. It has been demonstrated that the more potent a molecule is, the more likely it is to cause side effects, along with a prolonged onset of action, and vice versa.

The most concrete example is rocuronium, which has a rapid onset of action, but at the cost of reduced potency compared to other steroid-based agents.

Among the elements of toxicity, one can cite the case of pancuronium: due to its structure, the A-ring of the steroid nucleus is involved in a cardio-vagolytic effect, linked to its affinity for cardiac muscarinic receptors.

II.5 RELATIONSHIP BETWEEN CHEMICAL STRUCTURE AND PHARMACEUTICAL FORMULATION

Steroid-based neuromuscular blocking agents are naturally insoluble in water. However, the presence of positively charged quaternary ammonium groups can be exploited to prepare salts. This is the case with vecuronium bromide, where the addition of a bromide (Br^-), chloride (Cl^-), or sulfate ion increases the molecule's polarity, thereby making it more soluble in an aqueous medium.

Other methods can be used to improve the solubility of steroid-based neuromuscular blocking agents, including:

- The addition of solvents such as polyethylene glycol (PEG),
- Acidification, which stabilizes the charge and maintains solubility.

Some preparations also use cyclodextrins, which improves the solubility of rocuronium.

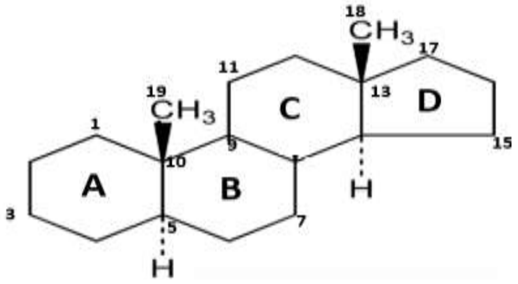
Conversely, excessive alkalization of a curare solution can cause precipitation, leading to a loss of solubility.

III. NOMENCLATURE OF STEROID-BASED NEUROMUSCULAR BLOCKING AGENTS

For the nomenclature of neuromuscular blocking agents, several synonyms exist. However, the standardized nomenclature of the International Union of Pure and Applied Chemistry (IUPAC) [25] remains the most widely used for assigning an appropriate name to each International Nonproprietary Name (INN) of a drug.

This literature review highlights the principal elements of the nomenclature of several steroid-based neuromuscular blocking agents, notably pancuronium, vecuronium, and rocuronium.

III.1 NOMENCLATURE OF THE STEROID NUCLEUS



The androstane steroid nucleus is derived from sterane and corresponds to a steroid comprising 19 carbon atoms. It exists in the form of a cyclopentanoperhydrophenanthrene. This nucleus consists of two systems:an ortho-condensed polycyclic hydrocarbon (phenanthrene),and a cyclic system (cyclopentane).

The perhydrophenanthrene nucleus comprises three rings, labeled A, B, and C, which are ortho-condensed, and attached to a fourth ring, the cyclopentane, called the D-ring.

The prefix "perhydro" indicates the complete saturation of the double bonds in the phenanthrene ring system. In total, the steroid nucleus includes 15 hydrogenations, located on carbon atoms numbered 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 14, 15, 16, and 17. The hydrogen with the lowest index is numbered 1 and denoted as H (1H); this is the indicated hydrogen. This indicated hydrogen is placed as a prefix in the nomenclature, itself preceded by the mention of the additional hydrogenation.

The numbering of the phenanthrene ring follows the rule for ortho-condensed polycyclic heterocycles. It begins from the ring at the far right (ring A or C), assigning the lowest index to one of the vertices. However, phenanthrene constitutes an exception to this rule due to its angular structure: in this case, the number 1 is assigned to a carbon at the angle, and the numbering then continues in a "Z" or zigzag pattern.

For the androstane ring system, numbering begins at the apex of ring A and proceeds in a zigzag pattern to conclude at ring D.

The methyl group borne by carbon C-13 is assigned the number 18, while the one located on carbon C-10 is assigned the number 19.

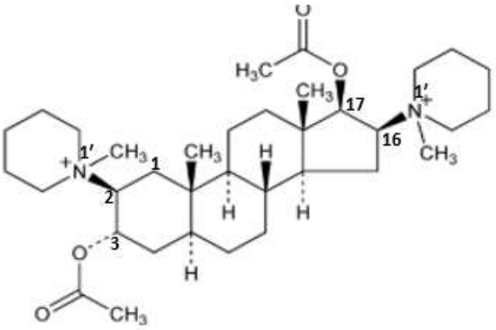
The side of the phenanthrene involved in the junction with ring D is designated, in the nomenclature, within brackets by the letters a, b, c,... following the numbering direction specific to phenanthrene.

Thus:
- [a] corresponds to side 1,2,
- [b] to side 2,3,
- [c] to side 3,4, and so on.

In the case of androstane, the D-ring is fused to the 1,2-side of the phenanthrene; it therefore receives the letter [a].

The standardized IUPAC chemical nomenclature for androstane is as follows: 10,13-dimethyl-2,3,4,5,6,7,8,9,11,12,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthrene.

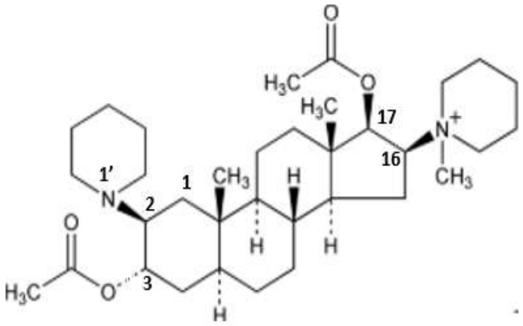
III.2 CHEMICAL NOMENCLATURE OF PANCURONIUM



-Main functional group :The molecule is in the form of a methyl ester, corresponding to an acetate.
-Base structure : Pancuronium is built on a base molecule which is androstane.

The complete name of this structure is: 2,3,4,5,6,7,8,9,11,12,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-3-yl.
This structure is attached to the main ester function via the carbon at position 3, which justifies the use of the suffix 3-yl.
-Substituents :At positions 2 and 16, the molecule bears two onium heterocycles, which are methylpiperidiniums. Each of these heterocycles contains a positively charged nitrogen atom, denoted as 1 (1-ium), itself substituted by a methyl group at position 1.
These two onium groups are directly attached to the base skeleton via their nitrogen atom, which justifies the use of the suffix 1-yl.
Their complete designation is therefore: 2,16-bis(1-methylpiperidin-1-ium-1-yl). At positions 10 and 13, there are two methyl groups. The substituents are listed in alphabetical order based on the first letter of each name. In this case, the two methyl groups are designated by the letter "m", while the piperidiniums are designated by the letter "p".
Thus, the correct order of listing is as follows: 10,13-dimethyl-2,16-bis(1-methylpiperidin-1-ium-1-yl). At position 17, there is an acetyloxy group.
In alphabetical order, the letter "A" for acetyloxy is considered, which places this substituent before the others.Le nom complet des substituants devient donc : 17-acetyloxy-10,13-dimethyl-2,16-bis(1-methylpiperidin-1-ium-1-yl).
The chemical name of pancuronium is: 17-acetyloxy-10,13-dimethyl-2,16-bis(1-methylpiperidin-1-ium-1-yl)-2,3,4,5,6,7,8,9,11,12,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-3-yl acetate.
According to IUPAC, the substituents are placed before the name of the parent chain, while the principal function is always expressed as a suffix, here in the form "acetate".

III.3 CHEMICAL NOMENCLATURE OF VECURONIUM

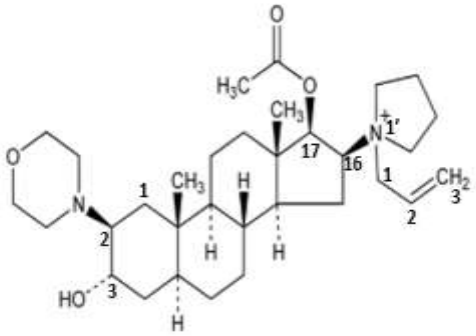


The structure of vecuronium is similar to that of pancuronium, except that vecuronium has only one quaternized nitrogen.
-Main functional group: ester function, it is an acetate.
-Base structure: similar to pancuronium.
-Substituents :The substituents are identical to those of pancuronium, except for the one at position 2, whose nitrogen atom is no longer quaternized.
This substituent corresponds to 2-piperidin-1-yl, meaning it is attached to vertex number 2 of the androstane via its nitrogen atom, which bears the index 1, hence the use of the suffix 1-yl.
The order of substituent listing follows the alphabetical order of the first letter of each name:
- a for acetyloxy,
- m for methyl and methylpiperidinium,
- p for piperidine.

Thus, the nomenclature of the substituents is written as follows: 17-acetyloxy-10,13-dimethyl-16-(1-methylpiperidin-1-ium-1-yl)-2-piperidin-1-yl.

The chemical name of vecuronium is: 17-acetyloxy-10,13-dimethyl-16-(1-methylpiperidin-1-ium-1-yl)-2-piperidin-1-yl-2,3,4,5,6,7,8,9,11,12,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-3-yl acetate.

III.4 CHEMICAL NOMENCLATURE OF ROCURONIUM



-Main functional group: ester function, it is an acetate.

-Base structure: similar to pancuronium.

-Substituents:At position 3, there is a hydroxyl group (-OH). At positions 10 and 13, two methyl groups (-CH_3). At position 2, a morpholine heterocycle is attached to the androstane skeleton via its atom at position 4, which justifies the use of the suffix 4-yl, giving morpholin-4-yl. Finally, at position 16, there is an onium group corresponding to pyrrolidin-1-ium.

The nitrogen atom being the heteroatom, it receives the lowest index (1).

This quaternary amine is substituted by a prop-2-en-1-yl group, which corresponds to an alkene chain with a double bond at position 2 and linked to the nitrogen via carbon number 1 (prefix 1-yl). Thus, the complete designation of this substituent is: 16-(1-prop-2-enylpyrrolidin-1-ium-1-yl).

The substituents are listed in the following alphabetical order: the letter "h" for hydroxy, the letter "m" for methyl, and the letter "o" for morpholine (the letter "m" in "methyl" is not disregarded in the actual IUPAC rules; this appears to be a clarification or correction). This yields the following substituents: 3-hydroxy-10,13-dimethyl-2-morpholin-4-yl-16-(1-prop-2-enylpyrrolidin-1-ium-1-yl).

The chemical name of rocuronium is: 3-hydroxy-10,13-dimethyl-2-morpholin-4-yl-16-(1-prop-2-enylpyrrolidin-1-ium-1-yl)-2,3,4,5,6,7,8,9,11,12,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-17-yl acetate.

IV. CONCLUSION

Neuromuscular blocking agents constitute an important family of drugs, both due to their pharmacological properties and the complexity of their chemical structures. This particularity has prompted researchers to study the relationships between chemical structure and pharmacological properties, particularly the elements of the structure-activity relationship. Several studies have thus been conducted to establish a link between the chemical structure and different parameters such as toxicity, metabolism, and, finally, neuromuscular blocking activity.

On a chemical level, although the nomenclature of neuromuscular blocking agents is complex, it remains homogeneous because it is based on a common chromophore: cyclopentanoperhydrophenanthrene, present in all steroid-based neuromuscular blocking agents.

According to the standard nomenclature of the International Union of Pure and Applied Chemistry (IUPAC), this core corresponds to 2,3,4,5,6,7,8,9,11,12,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthrenyl.

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