THE NORTHERN HOSPITAL

ROCURONIUM

"Brazilian Forest", oil on canvas, 1854, Martin Johnson Heade.

On the 5th of May we set off, to follow on foot our canoe, which had at length arrived, by the portage, at the Cano Pimichin. We had to ford a great number of streams; and these passages require some caution on account of the vipers with which the marshes abound….Esmeralda is the most celebrated spot on the Orinoco for the preparation of that active poison, which is employed in war, in the chase, and, singularly enough, as a remedy for gastric derangements. The poison of the ticunas of the Amazon, the upas-tieute of Java, and the curare of Guiana, are the most deleterious substances that are known. Raleigh, about the end of the sixteenth century, had heard of urari as being a vegetable substance with which arrows were envenomed (* In Tamanac marana, in Maypure macuri); yet no fixed notions of this poison had reached Europe. The missionaries Gumilla and Gili had not been able to penetrate into the country where the curare is manufactured. Gumilla asserts that this preparation was enveloped in great mystery; that its principal ingredient was furnished by a subterranean plant with a tuberous root, which never puts forth leaves, and which is called specially the root (raiz de si misma); that the venomous exhalations which arise from the manufacture are fatal to the lives of the old women who (being otherwise useless) are chosen to watch over this operation…When we arrived at Esmeralda, the greater part of the Indians were returning from an excursion which they had made to the east, beyond the Rio Padamo, to gather juvias, or the fruit of the bertholletia, and the liana which yields the curare. Their return was celebrated by a festival, which is called in the mission la fiesta de las juvias, and which resembles our harvest-homes and vintage-feasts. The women had prepared a quantity of fermented liquor; and during two days the Indians were in a state of intoxication. Among nations who attach great importance to the fruit of the palm, and of some other trees useful for the nourishment of man, the period when these fruits are gathered is marked by public rejoicings, and time is divided according to these festivals, which succeed one another in a course invariably regular…*

We were fortunate enough to find an old Indian more temperate than the rest, who was employed in preparing the curare poison from freshly-gathered plants. He was the chemist of the place. We found at his dwelling large earthen pots for boiling the vegetable juice, shallower vessels to favour the evaporation by a larger surface, and leaves of the plantain-tree rolled up in the shape of our filters, and used to filtrate the liquids, more or less loaded with fibrous matter. The greatest order and neatness prevailed in this hut, which was transformed into a chemical laboratory. The old Indian was known throughout the mission by the name of the poison-master (amo del curare). He had that self-sufficient air and tone of pedantry of which the apothecaries of Europe were formerly accused. "I know", said he, "that the Spaniards have the secret of making soap, and manufacturing that black powder which has the defect of making a noise when used in killing animals. The curare, which we prepare from father to son, is superior to anything you can make beyond the seas. It is the juice of an herb which kills silently, without anyone knowing whence the stroke comes". This chemical operation, to which the old man attached so much importance, appeared to us extremely simple. The liana (bejuco) used at Esmeralda for the preparation of the poison, bears the same name as in the forests of Javita…

The mavacure is employed fresh or dried indifferently during several weeks. The juice of the liana, when it has been recently gathered, is not regarded as poisonous; possibly it is so only when strongly concentrated. It is the bark and a part of the alburnum which

contain this terrible poison. Branches of the mavacure four or five lines in diameter are scraped with a knife, and the bark that comes off is bruised, and reduced into very thin filaments on the stone employed for grinding cassava. The venomous juice being yellow, the whole fibrous mass takes that colour. It is thrown into a funnel nine inches high, with an opening four inches wide. This funnel was of all the instruments of the Indian laboratory that of which the poison-master seemed to be most proud. He asked us repeatedly if, por alla (out beyond, meaning in Europe) we had ever seen anything to be compared to this funnel (embudo). It was a leaf of the plantain-tree rolled up in the form of a cone, and placed within another stronger cone made of the leaves of the palm-tree. The whole of this apparatus was supported by slight frame-work made of the petioles and ribs of palm-leaves. A cold infusion is first prepared by pouring water on the fibrous matter which is the ground bark of the mavacure. A yellowish water filters during several hours, drop by drop, through the leafy funnel. This filtered water is the poisonous liquor, but it acquires strength only when concentrated by evaporation, like molasses, in a large earthen pot. The Indian from time to time invited us to taste the liquid; its taste, more or less bitter, decides when the concentration by fire has been carried sufficiently far. There is no danger in tasting it, the curare being deleterious only when it comes into immediate contact with the blood. The vapours, therefore, which are disengaged from the pans are not hurtful, notwithstanding all that has been asserted on this point by the missionaries of the Orinoco... The most concentrated juice of the mavacure is not thick enough to stick to the darts; and therefore, to give a body to the poison, another vegetable juice, extremely glutinous, drawn from a tree with large leaves, called kiracaguero, is poured into the concentrated infusion.… this tree grows at a great distance from Esmeralda…

The curare is sold in little calabashes; but its preparation being in the hands of a few families, and the quantity of poison attached to each dart being extremely small, the best curare, that of Esmeralda and Mandavaca, is sold at a very high price. This substance, when dried, resembles opium; but it strongly absorbs moisture when exposed to the air. Its taste is an agreeable bitter, and M. Bonpland and myself have often swallowed small portions of it. There is no danger in so doing, if it be certain that neither lips nor gums bleed…. The process of this preparation appears to be everywhere nearly the same; but there is no proof that the different poisons sold by the same name at the Orinoco and the Amazon are identical, and derived from the same plants.... Possibly at some future day, one and the same alkaline principle, similar to morphine and strychnia, will be found in poisonous plants belonging to different genera…The danger of the curare, as of most of the other strychneae (for we continue to believe that the mavacure belongs to a neighbouring family), results only from the action of the poison on the vascular system…During our passage in returning from Esmeralda to Atures, I myself narrowly escaped an imminent danger. The curare, having imbibed the humidity of the air, had become fluid, and was spilt from an imperfectly closed jar upon our linen. The person who washed the linen had neglected to examine the inside of a stocking, which was filled with curare; and it was only on touching this glutinous matter with my hand, that I was warned not to draw on the poisoned stocking. The danger was so much the greater, as my feet at that time were bleeding from the wounds made by chegoes (Pulex penetrans), which had not been well extirpated. This circumstance may warn travellers of the caution requisite in the conveyance of poisons…The opinion is very general in the missions that no cure is possible, if the curare be fresh, well concentrated, and have stayed long in the wound, to have entered freely into the circulation. Among the specifics employed on the

banks of the Orinoco, and in the Indian Archipelago, the most celebrated is muriate of soda. (* Oviedo, Sommario delle Indie Orientali, recommends sea-water as an antidote against vegetable poisons. The people in the missions never fail to assure European travellers, that they have no more to fear from arrows dipped in curare, if they have a little salt in their mouths…*

Raleigh recommends as an antidote to the ourari (curare) the juice of garlic. [But later experiments have completely proved that if the poison has once fairly entered into combination with the blood there is no remedy, either for man or any of the inferior animals. The wourali and other poisons mentioned by Humboldt have, since the publication of this work, been carefully analysed by the first chemists of Europe, and experiments made on their symptoms and supposed remedies. Artificial inflation of the lungs was found the most successful, but in very few instances was any cure effected.] The wound is rubbed with this salt, which is also taken internally. I had myself no direct and sufficiently convincing proof of the action of this specific…Indians, who had been wounded in battle by weapons dipped in the curare, described to us the symptoms they experienced, which were entirely similar to those observed in the bite of serpents. The wounded person feels congestion in the head, vertigo, and nausea. He is tormented by a raging thirst, and numbness pervades all the parts that are near the wound. The old Indian, who was called the poison-master, seemed flattered by the interest we took in his chemical processes. He found us sufficiently intelligent to lead him to the belief that we knew how to make soap, an art which, next to the preparation of curare, appeared to him one of the finest of human inventions.

Alexander von Humboldt,
TRAVELS TO THE EQUINOCTIAL REGIONS OF AMERICA,
DURING THE YEARS 1799-1804. Chapter 2.24:
The Upper Orinoco, from the Esmeralda to the Confluence of the Guaviare.

The most famous Naturalist in the world, before the time of Charles Darwin, was the brilliant German polymath, Alexander von Humboldt. His tales of exploration of the great Amazon rain forests, travelling up the mighty Orinoco River captivated the imagination of all Europe and North America. Amoung his poetic and fabulous stories is the first scientific description of the poison much feared by the early Conquistadors - curare. Humboldt described in great detail his discussions with an Indian "chemist" who showed him how it was produced. The old poison-master thought the curare was the most important substance he produced…perhaps equal to the mysterious Spanish "Black powder" used in war…(or to Spanish soap as well, he added!). There was great fear of curare amoung the Europeans, who believed all manner of rumor about its powers. But Humboldt proved that it could only kill if it came in direct contact with the blood, and was otherwise harmless. He debunked all manner of supposed "specifics" (i.e antidotes), such as Raleigh's garlic extract or the colonist's "muriate of soda". No effective "specific" would be found until the development of neostigmine in the 20th century, and sugammadex in the 21st. Most presciently, he recognized that the only effective treatment was "artificial inflation of the lungs". Today a wide range of skeletal muscle paralyzing agents are used, not to kill, but in medicine to assist anesthesia and mechanical ventilation. Many of the agents used are direct derivatives of the poison-master's curare, one of the miraculous wonders of the staggering biodiversity of the Amazon.

ROCURONIUM

"...I will argue that every scrap of biological diversity is priceless, to be learned and cherished, and never to be surrendered without a struggle....We should preserve every scrap ....while we learn to use it and come to understand what it means to humanity".

Edward O Wilson.

Modern day non-depolarizing skeletal muscle relaxing drugs were developed from the curare vines of the deep Amazon. For centuries, South American Indians extracted and refined curare from them, the deadly agent of their terrifying poison arrows.

Introduction

Rocuronium is a non-depolarizing skeletal muscle relaxation agent used in anaesthesia and intensive care.

Its main advantage is a faster development of neuromuscular blockade compared to other non-depolarizing neuromuscular agents.

It can be used in high dose **for rapid sequence induction** and intubation in patients with a contraindication to suxamethonium, (such as **hyperkalemia**)

As for any non-depolarizing skeletal muscle relaxation agent rocuronium should only be used in association with full resuscitation and intubation equipment on hand and only by doctors experienced in managing intubation and anesthetized patients.

History

Modern day non-depolarizing skeletal muscle relaxing drugs were developed from the curare vines of the deep Amazon. For centuries, South American Indians extracted and refined curare from them, the deadly agent of their terrifying poison arrows.

Rocuronium was developed for clinical use in 1994.

Chemistry

Rocuronium bromide is a quaternary aminosteroid and an analogue of vecuronium bromide.

Rocuronium is a member of the **aminosteroid** class of skeletal muscle relaxing agents.

Physiology

There are two types of functionally different **acetylcholine** (or **cholinergic**) **receptors** (**AChR)** that bind acetylcholine and transmit its signal:

1. Muscarinic (named after the agonist muscarine):

   These are G-protein coupled receptors (GPCRs) that mediate a slow metabolic response via second messenger cascades.

   Muscarinic receptors are of 3 subtypes:

   - M1, M2, M3, M4 , M5

2. Nicotinic (named after the agonist nicotine):

   These are ligand-gated ion channels that mediate a fast synaptic transmission of the neurotransmitter.

   Nicotinic receptors are of two subtypes:

   - Nm:
     - ♥ This is located in the neuromuscular junction which causes the contraction of skeletal muscles by way of end-plate potential (EPPs).
   - Nn:

- ♥ This causes depolarization in autonomic ganglia resulting in post ganglionic impulses.

Classification

The skeletal muscle relaxing agents are broadly divided into two groups:

1. The depolarizing neuromuscular blockers:
   - Suxamethonium (or succinyl choline) (short acting)
2. The non-depolarizing neuromuscular blockers:
   - **The aminosteroids**:
     - ♥ Vecuronium (intermediate acting)
     - ♥ **Rocuronium** (intermediate acting)
     - ♥ Pancuronium (long acting)
   - **Benzyl-iso-quino-liniums**:
     - ♥ Atracurium (intermediate acting)
     - ♥ Cisatracurium (intermediate acting)
     - ♥ Mivacurium (intermediate acting)

Preparation

Ampoules:

- **5 ml ampoules of 50 mg, (i.e. 1 ml = 10 mg)**

Mechanism of Action

Rocuronium is an intermediate acting **non-depolarizing** neuromuscular blocking agent.

It acts by competitive inhibition of the natural neurotransmitter acetylcholine by blocking the nicotinic cholinoreceptors at the motor end plate of skeletal muscle.

Its action is antagonized by acetylcholinesterase inhibitors such as neostigmine.

In normal dose ranges it does not produce any clinically significant autonomic or cardiovascular effects.

At higher doses (1 mg/kg IV) there may be a mild increase in heart rate.

Pharmacodynamics

Onset and duration of action of rocuronium is **dose dependent**, with higher doses resulting in a quicker onset of action and a longer duration of action, (see dosing below).

Rocuronium like all the skeletal muscle paralysing agents has no sedative or analgesic effects, and should only be used in association with adequate anaesthesia.

Pharmacokinetics

Administration:

- IV bolus or by continuous infusion.
- Onset of action is rapid (relative to vecuronium) and at intubating doses (1.0 - 1.2 mg/kg) approaches that of suxamethonium.

Metabolism:

- Rocuronium is metabolized by the liver as well as excreted in the urine (and to a lesser extent, the bile).

  It is therefore eliminated much more slowly than suxamethonium which is relatively rapidly metabolized by pseudocholinesterase

Indications

1. Maintenance of paralysis in intubated patients.
2. In high dose for rapid sequence induction and intubation in patients with a contraindication to suxamethonium, (such as **hyperkalemia**)

Contraindications/ Precautions

1. Known severe hypersensitivity to rocuronium.
2. Rocuronium should only be used in association with full resuscitation and intubation equipment on hand and only by doctors experienced in managing intubation and anesthetized patients.
3. Myasthenia gravis: prolongs paralysis; avoid neuromuscular blocking agents if possible, (as with other non-depolarizing muscle relaxants).
4. **As for any non-depolarizing skeletal muscle relaxation agent rocuronium should only be used in association with full resuscitation and intubation**

equipment on hand and only by doctors experienced in managing intubation and anesthetized patients.

Adverse Effects

1 True anaphylaxis is very rare.

2. Anaphylactoid reactions (due to histamine release) may occur.

3. Prolonged use (> 48 hours) may result in an "ICU myopathy"

It has **not** been associated with malignant hyperthermia.

Dosing

- **Intubating dose (elective cases): 1.0 mg/kg IV**
  - ♥ This dosing will generally have a slower onset of action compared to suxamethonium.
- **Intubating dose (emergent RSI cases): 1.2 mg/kg IV**
  - ♥ This dosing will provide a quicker onset of action (similar to that of suxamethonium, i.e 45-60 seconds)

    A more rapid onset of action is important in situations of emergency RSI.
- Standard loading dose (intubated patients): **0.6 mg/kg IV**
- Maintenance dosing: **0.20 mg/kg IV**

The higher the dose the shorter will be the onset of action as well as the longer the duration.

1.2 mg/kg IV loading dose will have a duration of action of around 90 minutes.

1 mg/kg IV loading dose will have a duration of action of 60 minutes.

0.6 mg/kg IV loading dose will have a duration of action of 30 minutes.

Note that at doses greater than 1.0 mg/kg IV, intubating *conditions* will not appreciably improve, however the onset and duration of action will be longer.

There is no accumulation of effect (progressive increase in duration of action) with repetitive dosing at the recommended levels of dosing.

Maintenance infusions:

- 0.3 - 0.6 mg/kg/hour after early evidence of spontaneous recovery from the bolus dose; adjust according to response.

Reversal:

For reversal:

- Complete reversal is usually achieved within **8-10 minutes** of **neostigmine** administration with most of the non-depolarizing agents (except pancuronium)

AND

- An anticholinergic, e.g. **atropine** (or gylcopyrrolate), to prevent the muscarinic effects of neostigmine (especially bradycardia).

For adults give:

- Neostigmine: **2.5 mg IV.**

Plus

- Atropine: **1.2 mg IV**

Alternatively:

- The neuromuscular block of **Rocuronium** (or vecuronium) can also be reversed by **sugammadex**, a Selective Relaxant Binding Agent.

  The main advantage of sugammadex is reversal of neuromuscular blockade without relying on inhibition of acetylcholinesterase. It directly combines with rocuronium.

  Therefore it does not cause the autonomic instability produced by anticholinesterases such as neostigmine, and antimuscarinic agents such as atropine do not need to be co-administered.

  Its administration is therefore associated with much greater cardiovascular and autonomic stability than the traditional reversal agents.

  It is also quick acting compared to neostigmine. It can reverse the effects of rocuronium in about **2 minutes.**

  It is a better reversal option than neostigmine and atropine in cases where intubation has failed and a quick reversal is desired.

"Portrait of Alexander von Humboldt", oil on canvas, 1806, Friedrich Georg Weitsch

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