THE NORTHERN HOSPITAL

ROPIVACAINE

William Pitt the Younger, (detail) oil on canvas, Gainsborough Dupont, 1788

"I have never seen so much fortitude and courage in all my practice"

John Hunter, Surgeon Extraordinary to King George III, 1783.

William Pitt the Younger was one of Britain's greatest statesmen. In 1783, at the extraordinary age of just twenty-four, he became (and so remains) the youngest Prime Minister in the history of England. Not only was he the youngest Prime Minister, however he was also one of England's greatest. He led Britain and the Empire through a period of great turmoil during the late Eighteenth and early Nineteenth centuries, steering a course through the great crises of the period, from the madness of King George III, the French revolution and the Napoleonic wars during which he became the country's longest ever war time serving Prime Minister. He oversaw the controversial "act of union" which saw the unification of England and Ireland to become the "United Kingdom" in 1800. He rehabilitated the nation's disastrous financial situation following the American War of Independence.

Today he is remembered as possibly Britain's greatest Prime Minister at least until the time of Winston Churchill. Though he did Britain proud, it would be at the expense of his physical and mental health. In early 1786, however his health was excellent except for a disfiguring "growth" or "cyst" on his cheek. He took the decision that it had to be removed. As difficult as it is for us to comprehend in the 21st century, the decision to have a relatively minor lesion removed surgically from the body was one not one to be taken lightly. In an age without anesthesia, tetanus immunoprophylaxis or antibiotics, procedures that we would regard today as minor, could be life threatening in the Eighteenth century. The only anesthesia available was liberal amounts of alcohol and opiates which would often lead to dangerous overdose, even death in its own right. The patient was kept still by sturdy assistants who would tie and restrain the patient. If infection set in, there was no treatment. Any surgical procedure took a great deal of courage on the part of not only the patient but also of the surgeon.

For so important a figure as the British Prime Minister, only the very best available surgeon would be trusted. The great John Hunter, Surgeon Extraordinary to King George III, was the man called in to do the job. He carefully explained to the Prime Minister the risks of the procedure and the pain that he would have to endure. Pitt said he understood and consented to have the procedure performed. He conducted himself just as he did so for the weighty affairs of the state… magnificently. He refused to have his hands tied and during the procedure sat motionless with his eyes fixed on the Horseguards clock, having been told the operation would take six minutes. Despite the agony Pitt did not flinch or cry out once. Hunter was so impressed with his patient he was moved to comment later that he had never seen "so much fortitude and courage in all his practice".

Pitt's only reaction came at the very end of the procedure with the comment, "Sir, you have exceeded your time half a minute!"

In the 21st century the ordeal of local surgery in now a simple matter thanks to one of the modern miracles of pharmacology, the amide and ester local anesthetic drugs. The medical profession of the Eighteenth century would have regarded these drugs as truly miraculous. With agents such as ropivacine, William Pitt would have had no need to admonish his surgeon over his extra half minute!

ROPIVACAINE

Ampoule of Ropivacaine 0.75 % (150 mg)

Introduction

Ropivacaine is an amide local anaesthetic agent.

It is a long-acting analogue of bupivacaine produced as the pure S-enantiomer, and has number of advantages over bupivacaine which include:

- Lower arrhythmogenic effects.
- Less cardiac depressant effects.
- It has greater differential in the response of sensory and motor nerves to local anaesthetic blocks.

  At lower doses it produces sensory block and analgesia while at higher doses it can produce surgical anaesthesia with motor block.

In the ED it is a useful agent for large nerve peripheral nerve blocks.

History

The Nobel Prize in Physiology or Medicine for 1963 was awarded jointly to **Sir John Carew Eccles, Alan Lloyd Hodgkin** and **Andrew Fielding Huxley.**

By studying the giant axons of two squid species ***Loligo forbesii*** and ***Doryteuthis pealeii,*** they were able to determine the nature of the nerve action potential. Their discoveries remain one of the greatest in the history of biology, and rank among the most significant conceptual breakthroughs in the neurosciences.

Later studies utilized tetrodotoxin to further understand the nature of the action potential in excitable tissue.

Tetrodotoxin is a natural lethal toxin found in **pufferfish** that specifically inhibits the voltage-sensitive sodium channel, responsible for the initiation and propagation action potentials.

Ropivacaine was essentially developed after bupivacaine was noted to be associated with significant toxicity including, cardiac arrest if inadvertently given IV.

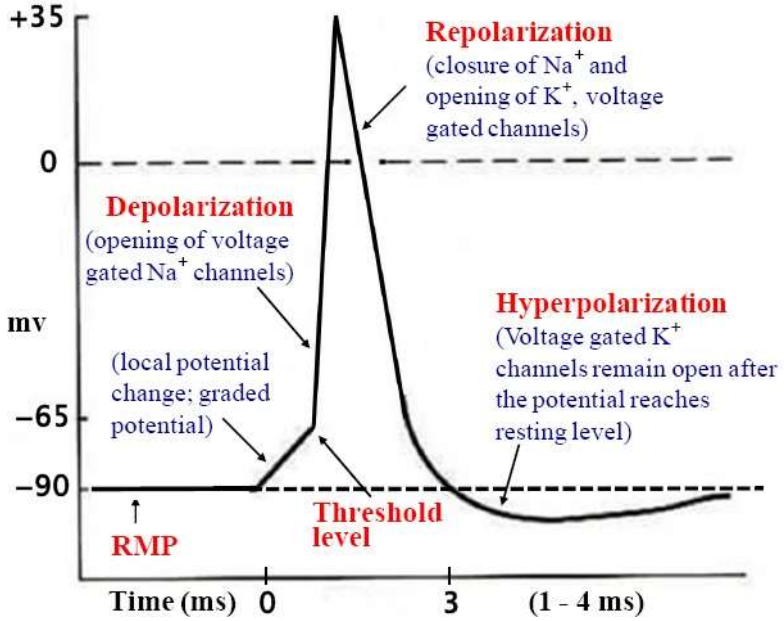
Ropivacaine was found to have less cardiotoxicity than bupivacaine in animal models

Chemistry

Ropivacaine is an amide anaesthetic agent.

It is a long-acting analogue of bupivacaine

Physiology



The nerve action potential. Local anaesthetic drugs are sodium channel blocking agents.

Classification

Local anaesthetic agents are classically divided into two principal classes:

1. Amides:
    - Bupivacaine
    - Levobupivacaine
    - Lignocaine
    - Prilocaine
    - **Ropivacaine**
2. Esters:
    - Amethocaine
    - Oxybuprocaine
    - Cocaine

Preparation

Ropivacaine hydrochloride as:

Ampoules:

- 0.75% (7.5 mg/mL) in 20 mls

  This is 150 mg in one ampoule.

Fixed-dose combination with fentanyl:

- Epidural infusion for analgesia

Pharmacodynamics [2]

Onset of action:

- Topical/infiltration: 10 -15 minutes.
- Nerve blockade 15 - 30 minutes

- ♥ Note that onset of action of nerve blockade however also depends on the size of the nerve; complete blockade takes longer with larger nerves.

Duration of action:

- Topical: 30 minutes - 1 hour.
- Infiltration: 3 - 4 hours
- Minor nerve block 2 - 6 hours.
- Major nerve block: 7 - 14 hours
- Epidural 3 - 4 hours.

Pharmacokinetics

Absorption

- Ropivacaine can be administered by local infiltration or by epidural infusion.
- It must **never** be used intravenously.

Distribution

- There is high protein binding, (up to 94 %)
- Excretion into breast milk occurs
- Human placental transfer can occur

Metabolism

- Ropivacaine is an aminoamide local anaesthetic and these are less water soluble, when compared to the aminoester local anaesthetics and they are primarily metabolized in the liver by de-ethylation.

  Aminoester local anaesthetics such as procaine and amethocaine on the other hand are more water soluble, than the aminoamides and are primarily metabolised in plasma by pseudocholinesterases.

Mechanism of Action

Local anesthetics block nerve conduction by preventing the increase in membrane permeability to sodium ions that normally leads to a nerve impulse.

As for other local anaesthetic agents ropivacaine acts by the reversible blockade of fast sodium channels.

The progression of local anaesthetic block relates to:

- Nerve fiber diameter
- Myelination
- Conduction velocity.

In general, loss of nerve function occurs in the following order:

- Loss of autonomic activity
- Loss of pain sensation.
- Loss of other sensory modalities
- Motor activity.

Indications

Major peripheral nerve blocks that require prolonged duration of action.

These include:

1. Infiltration, nerve block
2. Epidural / intrathecal anaesthesia

Contraindications/ Precautions

These include:

1. Due to the potential for systemic toxicity, ropivacaine is contraindicated:
    - For IV use
    - For use in intravenous regional anaesthesia (ie Bier's block).
2. Local infection
3. Combative / uncooperative patients
4. Known allergy

Pregnancy

Ropivacaine is classified as a category B1 drug with respect to pregnancy.

Category B1 drug are those drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have not shown evidence of an increased occurrence of fetal damage.

From the limited information available, maternal use of ropivacaine has not been associated with adverse pregnancy outcomes .

Ropivacaine is considered safe to use at the lowest effective dose during pregnancy for neuraxial analgesia or anaesthesia. [4]

Breast feeding

Ropivacaine is safe to use during breastfeeding.

Ropivacaine has a short elimination half-life and poor oral bioavailability. Small amounts of ropivacaine are excreted into breast milk, but no serious harmful effects have been reported in breastfed infants. [4]

Adverse Effects

Initial symptoms are usually neurological unless there has been a large intravenous bolus where cardiac arrhythmia or arrest may be the first manifestation of toxicity.

1. Early neurological symptoms include:

    - Dizziness
    - Anxiety/ agitation / confusion
    - Peri-oral parasthesia or numbness.
    - Tinnitus

More severe toxicity will produce cardiac and more serious neurological symptoms:

2. CNS:

    - Seizures

- Coma

3. CVS:

   - Bradycardia
   - Hypotension
   - Arrhythmias, which may be lethal VT/ VF or asystole.

4. Respiratory:

   - Respiratory depression.

Other adverse rare effects may include:

5. Methaemoglobinaemia:

   - This manifests as cyanosis and the signs of hypoxia

   See also separate document on Methaemoglobinaemia

6. Allergic reactions:

   - Allergic reaction to local anaesthetic drugs can occur within the same chemical group, i.e esters or amides.

     Allergic reactions are rare, but are relatively more common with esters than with amides.

     There is no cross-reactivity between the two groups.

     Reactions may present as localised oedema, urticaria, bronchospasm and frank anaphylaxis.

     Rash may occur following skin application.

Dosing

The addition of adrenaline confers *no* advantage in the clinical use of ropivacaine.

The maximum recommended dose is **3 mg/kg** per single dose (> 200 mg is rarely needed)

References

1. eTG - July 2016

2. Ropivacaine in Australian Medicines Handbook Website Accessed December 2016.

3. Ropivacaine in MIMs Website 1 July 2011.

4. Ropivacaine in RWH Pregnancy & Breastfeeding Guidelines, 14 January 2016.

Further reading:

William Pitt the Younger, William Hague, Alfred A Knopf, 2005.

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