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Newer Local anesthetics

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Abstract

Local anesthetics have a wide range of applications ranging from acute pain during labour to heart and lung surgeries. Newer local anesthetics have been developed with longer duration of action and the drawbacks of traditional local anesthetic like bupivacaine. This article describes in brief the newer local anesthetics and their mechanisms.

Keywords: *local anesthetic ,history, mechanism of action, chemical structure, ropivacaine, levobupivacaine*

INTRODUCTION

The word 'anesthetic' comes from the Greek word meaning the absence or loss of sensation. Local anesthesia is defined as "a reversible loss of sensation in a circumscribed area of the body caused by a depression of excitation in nerve endings or an inhibition of the conduction process in the peripheral nerves" [1] . The use of local anesthetic decreases the post operative pain, need for general anesthesia and increases the patients cooperation.

HISTORY

Local anesthesia was discovered by a young Viennese ophthalmologist discovered that cocaine which he instilled into his own conjunctival fornix produced loss of sensitivity to touch and injury [2]. On September 11, 1884, he performed the first operation using local anesthetic on a patient with glaucoma. [3]

As the effects of cocaine (toxicity, addiction, and others) gradually became known, new anesthetic drugs were sought to replace. In November 27, 1904, German chemist Alfred Einhorn developed novocaine. [4] In 1943–1946, Nils Löfgren and Bengt Lundquist developed a xylidine derivative they called lidocaine, whose action is longer and safer compared to novocaine [5].Nowadays newer local anesthetic drugs like ropivacaine and levobupivacaine are used.

MECHANISM OF ACTION

All local anesthetics are membrane stabilizing drugs. They reversibly decrease the rate of depolarization and repolarization of excitable membranes . Local anesthetic drugs act mainly by inhibiting sodium influx through sodium-specific ion channels in the neuronal cell membrane, in particular the so-called voltage-gated sodium channels. When the influx of sodium is interrupted, an action potential cannot arise and signal conduction is inhibited. The receptor site is thought to be located at the cytoplasmic (inner) portion of the sodium channel. Local anesthetic drugs bind more readily to sodium channels in an activated state, thus onset of neuronal blockade is faster in neurons that are rapidly firing. This is referred to as state dependent blockade. ([6]- [8]) Voltage-dependent and voltage-independent K^+ channels and voltage-dependent Ca^{2+} channels are also blocked by local anesthetics.([9]- [12])

CHEMICAL STRUCTURE

The injectable local anesthetic in dentistry contains a hydrophilic aromatic terminal, intermediate chain and a lipophilic component. [13] The hydrophilic portion of constitutes of either a secondary or tertiary amine. Based on the intermediate chain present, the local anesthetics are classified as amide or esters. [14]

ROPIVACAINE

Ropivacaine (*N*-*n*-propyl 2′,6′-pipecoloxylidide) is an amino-amide local anaesthetic. It was first registered for clinical use in 1996. [15] It is less cardio toxic than bupivacaine.

STRUCTURE

Enantiomers exist in two different spatial configurations, like right- and left-handed gloves, and are present in equal amounts in a racemic solution. They are optically active and can be differentiated by their effects on the rotation of the plane of a polarised light into dextrorotatory [clockwise rotation (R+)] or levorotatory [counterclockwise rotation (S-)] stereoisomers. The physicochemical properties of the two enantiomeric molecules are identical, but the two

enantiomers can have substantially different behaviors in their affinity for either the site of action or the sites involved in the generation of side effects. Ropivacaine is an optically pure S(-) enantiomeric from the parent chiral molecule propivacaine. [16]

PHARMACODYNAMICS AND PHARMACODYNAMICS

Ropivacaine is less lipophilic compared to bupivacaine so it is less cardio toxic and has a higher threshold for CNS toxicity.([17], [18]) It inhibits platelet aggregation at concentrations of 3.75 and 1.88 mg/ml. [19]

The plasma concentration of ropivacaine depends on the total dose administered and the route of administration, as well as the hemodynamic and circulatory condition of the patient and vascularity of the administration site. When ropivacaine was administered intravenously in subjects, its pharmacokinetics were linear and dose proportional up to 80 mg. The absorption of ropivacaine 150 mg from the epidural space is complete and biphasic. The mean half-life of the initial phase is approximately 14 minutes, followed by a slower phase with a mean absorption $t_{1/2}$ of approximately 4.2 hours Ropivacaine is bound to plasma proteins to an extent of 94% ([20], [21])

CLINICAL USES

Ropivacaine is indicated for local anesthesia including infiltration, nerve block, epidural and intrathecal anesthesia in adults and children over 12 years. It is also used for peripheral nerve block and caudal epidural in children 1–12 years for surgical pain. It is also sometimes used for infiltration anesthesia for surgical pain in children. Ropivacaine is often co administered with fentanyl for epidural analgesia, in pregnant women during labour. [22]

ADVERSE EFFECTS

Adverse drug reactions (ADRs) are rare when it is administered correctly. Most ADRs relate to administration technique (resulting in systemic exposure) or pharmacological effects of anesthesia, however allergic reactions can rarely occur.

Systemic exposure to excessive quantities result in central nervous system (CNS) and cardiovascular effects – CNS effects usually occur at lower blood plasma concentrations and additional cardiovascular effects present at higher concentrations. CNS effects may include CNS excitation (nervousness, tingling around the mouth, tinnitus, tremor, dizziness, blurred vision, seizures followed by depression (drowsiness, loss of consciousness), respiratory depression and apnea).Cardiovascular effects include hypotension, bradycardia, arrhythmias, and/or cardiac arrest – some of which may be due to hypoxemia secondary to respiratory depression. [23]

Clinically adequate doses of ropivacaine are related with a lower incidence or grade of motor

block than bupivacaine. Thus, ropivacaine, with its efficacy, lower propensity for motor block, and reduced potential for CNS toxicity and cardio toxicity, is an important option for regional anesthesia and management of postoperative and labour pain.

LEVOBUPIVACAINE STRUCTURE

Levobupivacaine is an enantiomer of the long-acting local anaesthetic bupivacaine, which, although currently the most widely used agent in surgery and obstetrics, is associated with potentially fatal cardio toxicity. [24]

PHARMACODYNAMICS AND PHARMACOKINETICS

The intravascular dose of levobupivacaine required to cause lethality in animals is consistently higher compared with bupivacaine... In the studies conducted using surrogate markers of both cardiac and CNS toxicity levobupivacaine or bupivacaine were given by intravascular injection to healthy volunteers. Levobupivacaine was found to cause smaller changes in indices of cardiac contractility and the QTc interval of the electrocardiogram and also to have less depressant effect on the electroencephalogram. [25]

CLINICAL USES

Levobupivacaine is used for local anesthesia including infiltration, nerve block, ophthalmic, epidural and intrathecal anesthesia in adults; and infiltration analgesia in children. [26]

ADVERSE EFFECTS

CNS effects usually occur at lower blood plasma concentrations and additional cardiovascular effects present at higher concentrations, though cardiovascular collapse may also occur with low concentrations. CNS effects may include CNS excitation (nervousness, tingling around the mouth, tinnitus, tremor, dizziness, blurred vision, seizures) followed by depression (drowsiness, loss of consciousness, respiratory depression and apnea). Cardiovascular effects include hypotension, bradycardia, arrhythmias, and/or cardiac arrest – some of which may be due to hypoxemia secondary to respiratory depression. [23]

Levobupivacaine is a long acting local anaesthetic with a clinical profile closely resembling that of bupivacaine. However, current preclinical safety and toxicity data show an advantage for levobupivacaine over bupivacaine. Clinical data comparing levobupivacaine with ropivacaine are needed before the role of the drug can be fully established.

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