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A REVIEW ON LOCAL ANAESTHETICS

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ABSTRACT

Local anaesthesia is the simplest form of anaesthesia. It is defined as the infiltration of local anaesthesia, usually lidocaine, directly into the tissues, causing numbness of the skin and surrounding tissue targeted for surgery, with or without outpatient oral medication for analgesia, sedation or to reduce anxiety. This definition of local anaesthesia allows for the use of medication approved for patient self-administration at home. When used properly, local anaesthetics are safe and have few major side effects. However, in high doses, local anaesthetics can have toxic effects caused by their being absorbed through the blood stream into the rest of the body, so-called systemic toxicity. This may significantly affect breathing, heartbeat, blood pressure and other body functions.

INTRODUCTION

Local anaesthetic drugs are used widely for the provision of anaesthesia and analgesia both intra- and post-operatively. Understanding the pharmacology of these agents as a group, as well as the differences between specific drugs, enables the anaesthetist to use them safely to maximum effect.

Local anaesthetics produce a reversible loss of sensation in a portion of the body. Local anaesthetics may be used as the sole form of anaesthesia, in combination with general anaesthesia, and/or to provide postoperative analgesia.

Definition of a local anaesthetic

A local anaesthetic can be defined as a drug which reversibly prevents transmission of the nerve impulse in the region to which it is applied, without affecting consciousness. There are many drugs which exert local anaesthetic activity in addition to their main clinical uses, but this tutorial will focus on those drugs which are principally used for their local anaesthetic properties.

History

1. **1860-** Albert Niemann isolated crystals from the coca shrub – and called it "cocaine" – he found that it reversibly numbed his tongue! Sigmund Freud became aware of the mood altering properties of cocaine, and thought it might be useful in curing morphine addiction. Freud obtained a supply of cocaine (from Merck) and shared it with his friend Carl Koller, a junior intern in ophthalmology at the University of Vienna.
2. **1884-** Preliminary experiments using conjunctival sacs of various animals species, Koller did first eye surgery in humans using cocaine as local anesthetic.
3. **1905-** German chemist Alfred Einhorn produced the first synthetic ester type local anesthetic - novocaine (procaine) - retained the nerve blocking properties, but lacked the powerful CNS actions of cocaine.
4. **1943-** Swedish chemist Nils Lofgren synthesized the first amide-type local anesthetic - marketed under the name of xylocaine (lidocaine).

Structural classification of local anaesthetics

The basic chemical structure of a local anaesthetic molecule consists of 3 parts:

1. Lipophilic group- an aromatic group, usually an unsaturated benzene ring.
2. Intermediate bond- a hydrocarbon connecting chain, either an ester (-CO-) or amide (-HNC-) linkage. The intermediate bond determines the classification of local anaesthetic.
3. Hydrophilic group- a tertiary amine and proton acceptor.

Amide and ester local anaesthetics follow different paths of metabolism. Ester local anaesthetics are more likely to cause an allergic reaction. In the operating room we don't have the opportunity to examine the chemical structure. An easy way to tell the difference between an ester and amide is to determine if the generic name has an "i" before the "–caine". This„ trick" will only work with generic name…it will not work with the trade or commercial name. All amide local anaesthetics contain an "i" in the name. For example, lidocaine, mepivacaine, prilocaine, bupivacaine, ropivacaine, and levo-

bupivacaine all contain an "i" before the "-caine". Esters such as procaine, chloroprocaine, and tetracaine do not contain an "i" before the "-caine".

Pharmacological Data

Esters	Max Dose (mg/kg)	Duration (h)
Chloroprocaine	12	0.5 – 1
Procaine	12	0.5 – 1
Cocaine	3	0.5 – 1
Tetracaine	3	1.5 – 6

Amides	Max Dose (mg/kg)	Duration (h)
Lidocaine	4.5/(7 with epi)	0.75 – 1.5
Mepivacaine	4.5/(7 with epi)	1 – 2
Prilocaine	8	0.5 – 1
Bupivacaine	3	1.5 – 8
Ropivacaine	3	1.5 – 8

Local anaesthetics as isomers

Local anaesthetics may also be considered in terms of their stereoisomerism. This term describes the existence of molecules with the same molecular and structural formula, but different spatial orientation around a particular atom, the chiral centre. This is like the right and left foot being mirror images of each other. Stereoisomerism occurs in the case of bupivacaine which has two stereoisomers, known as R and S forms, and also in the case of prilocaine. The combination of equal amounts of the two stereoisomers of a particular drug is known as a racemic mixture.

The mechanism of action of local anaesthetics

Local anaesthetics disrupt ion channel function within the neurone cell membrane preventing the transmission of the neuronal action potential. This is thought to occur via specific binding of the local anaesthetic molecules (in their ionised form) to sodium channels, holding them in an inactive state so that no further depolarisation can occur. This effect is mediated from within the cell; therefore the local anaesthetic must cross the cell membrane before it can exert its effect. A second mechanism is also thought to operate, involving the disruption of ion channel function by the incorporation of local anaesthetic molecules into the cell membrane (the membrane expansion theory). This is thought to be mediated mainly by the unionised form acting from outside the neuron. Nerve fibres differ in their sensitivity to local anaesthetics. Small nerve fibres are more sensitive than large nerve fibres while myelinated fibres are blocked before non-myelinated fibres of the same diameter. Thus the loss of nerve function proceeds as loss of pain, temperature, touch, proprioception, and then skeletal muscle tone. This is why people may still feel touch but not pain when using local anaesthesia.

Pharmacokinetics of local anaesthetics

Absorption and distribution Local anaesthetic drugs are administered to the areas around the nerves to be blocked – which include skin, subcutaneous tissues, intrathecal and epidural spaces. Some of the drug will be absorbed into the systemic circulation: how much will depend on the vascularity of the area to which the drug has been applied and intrinsic effects of the drug or its additives on vessel diameter. Some local anaesthetics have vasodilatory effects at low concentrations, increasing their systemic absorption. This is countered in some preparations which include a vasoconstrictor such as adrenaline or felypressin. Cocaine, in contrast, has a vasoconstrictive effect. The distribution of the drug is influenced by the degree of tissue and plasma protein binding of the drug. The more protein bound the agent, the longer the duration of action as free drug is more slowly made available for metabolism.

Metabolism and excretion

Ester and amide anaesthetics differ in their metabolism. Esters (except cocaine) are broken down rapidly by plasma esterases to inactive compounds and consequently have a short half-life. Cocaine is hydrolysed in the liver. Ester metabolite excretion is renal. Amides are metabolised hepatically by amidases. This is a slower process, hence their half-life is longer and they can accumulate if given in repeated doses or by infusion. Prilocaine is also metabolised extra-hepatically.

Clinical uses of local anaesthetics

Local anaesthetics are available as solutions for injection, sprays, creams and gels. They are prepared as the hydrochloride salt to enable them to be dissolved in water (resulting in an acidic solution). Of note, due to new legislation, some of the newer local anaesthetics are described in terms of the quantity of free base present alone, in contrast to the older drugs which are described in terms of the quantity of total hydrochloride salt present. This is why, for example, 10ml of 0.5% bupivacaine (a racemic mixture) contains fewer local anaesthetic molecules than 10ml of 0.5% levobupivacaine. Most local anaesthetic preparations

contain a preservative agent such as 0.1% sodium metabisulphite, with or without a fungicide. Multidose vials contain 1mg/ml of the preservative methyl parahydroxybenzoate. The drug may also be combined (by the manufacturer or in some cases the clinician) with other local anaesthetics (e.g. EMLA cream - eutectic mixture of local anaesthetics) or additives designed to enhance their effects. These include adrenaline 1/200,000, bicarbonate (e.g. 0.15ml of 8.4% solution added to 10ml 0.5% bupivacaine) or glucose (usually 80mg/ml).

Adverse Effects of Local Anaesthetics

Anaesthetics are medications designed to help manage pain by either decreasing pain to tolerable levels or blocking pain. Local anaesthesia affects the specific body part where it is administered. This form of anaesthesia does not induce unconsciousness and is usually administered via injection, although local anaesthesia is also available in nasal spray and gel form.

1. **Haemorrhaging and infection:** Local anaesthesia may cause haemorrhaging or bleeding when administered via injection. The injection site may become infected. Nevertheless, the chances of excessive bleeding and infection are low, especially if the proper precautions are taken.
2. **Impaired mental clarity:** Normal mental functions can become impaired by local anaesthesia. This is because local anaesthesia can impede the ability to think clearly due to possible unintended psychotropic effects. The precise duration and degree of impaired mental clarity may vary depending on the specific local anaesthesia used. Nevertheless, until the effects of the local anaesthesia have worn off, significant decisions should be postponed.
3. **Impaired respiratory function:** Respiratory function may be impaired by local anaesthesia. The specific degree to which respiratory function is impaired depends on the kind of local anaesthesia used. The patient's medical history, local anaesthesia type and dosage should be considered carefully prior to administering local anaesthesia.
4. **Neural damage:** Local anaesthesia may cause long-term neural damage. However, such a side effect is uncommon.
5. **Allergic reaction:** Using local anaesthesia carries the risk of a possible allergic reaction. Nevertheless, the risk of this side effect occurring can be greatly reduced if factors such as medical history and patient allergies to medication are thoroughly considered prior to administering the local anaesthesia.
6. **Pain:** Pain may not be blocked completely by local anaesthesia. The reasons for this are varied. Switching from local to general anaesthesia may be necessary if the pain experienced exceeds the patient's tolerance level.
7. **Prolonged anaesthetic effects:** Local anaesthesia may take a longer time than expected. This side effect depends upon the patient and type of local anaesthesia used.
8. **Swelling of affected area:** Swelling may occur at the site where the local anaesthesia was administered.
9. **Temporary impaired movement:** Local anaesthesia can impair movement and the overall utility of the affected area. The muscles in the affected area may be unresponsive and may even feel weaker than usual.

Applications of local anaesthesia

1. **Nerve block:** Injected locally to produce regional anaesthesia (e.g., dental and other minor surgical procedures)
2. **Topical application**: To skin for analgesia (e.g., benzocaine) or mucous membranes (for diagnostic procedures)
3. **Spinal anaesthesia**: Injection into CSF to produce anaesthesia for major surgery (e.g., abdomen) or childbirth
4. **Local injection:** At end of surgery to produce long-lasting post-surgical analgesia (reduces need for narcotics)
5. **I.V. infusion*:*** For control of cardiac arrhythmias (e.g., lidocaine for ventricular arrhythmias)

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