A REVIEW ON LOCAL ANESTHETIC SUSTAINED-RELEASE PAIN MANAGEMENT

Sonal Satish Khandagale, Snehal Balkrushna Thombre, Anjali Vijendra Rathod, Prerna Prakash Vaishnav, Sanskruti Sandeep Lembhe, Shalini Kisan Kawade, Abhijeet Baburao Pawale.
Gajanan Maharaj College Of Pharmacy, Chh. Sambhajinagar
Khandagalesonal5@gmail.com
Prof. Shubhangi D. Bhojgude (M pharm), Department of Pharmaceutics,
Dr. Kavita Kulkarni (phd.M.Pharm), Department of Quality Assurance, Gajanan Maharaj College Of Pharmacy, Chh. Sambhajinagar.

Abstract :

One of the most prevalent and mostly unaddressed clinical issues in modern medicine is pain management. The use of local anaesthetics in pain management is essential. The short duration of a single injection is the primary drawback of conventional local anaesthetics. For many years, medicine's main focus has been on treating both acute and chronic pain. In order to properly control pain in surgery and post-surgical settings, doctors have attempted to create new strategies. To solve this issue, catheters are frequently inserted or combined with other medications in clinical practice to extend the time that local anaesthetics work.

Effective pain management, particularly for acute and chronic conditions, remains a significant clinical challenge, primarily due to the limited duration of action of traditional local anesthetics. To address this issue, various advanced drug delivery systems have been developed, including injectable responsive hydrogels and extended-release formulations like SABER-Bupivacaine, which provide prolonged analgesia for up to 72 hours while minimizing opioid consumption.

Recent studies highlight the efficacy of bupivacaine/meloxicam combinations in postoperative pain management, demonstrating enhanced analgesic effects compared to standard treatments. Additionally, novel agents such as tetrodotoxin and neosaxitoxin are being explored for their potential to extend the duration of anesthesia.

Current research trends emphasize the development of safer, long-acting local anesthetics and the repurposing of existing drugs to enhance therapeutic outcomes. These advancements represent promising avenues for improving pain management strategies in clinical practice, potentially transforming patient care.

Key words :*Pain management, local anesthetics, extended-release system, HTX-011a, Bupivacaine, Meloxicam, Mepivacaine, Novel Local Anesthetics, Peripheral Nerve Blocks, Postoperative pain, long-acting local anesthetic*

INTRODUCTION

Local Anesthetics :

A local anesthetic (LA) is a medication that causes absence of all sensation in a specific body part without loss of consciousness, providing local anesthesia, as opposed to a general anesthetic, which eliminates all sensation in the entire body and causes unconsciousness. Local anesthetics are most commonly used to eliminate pain during or after surgery.

How Local Anesthetics works :

- Local anaesthetics prevent nerves in a specific portion of your body from transmitting impulses to your brain.
- You will not feel any pain after receiving a local anesthetic, but you may feel some pressure or movement.

- It usually takes only a few minutes to decrease sensation in the area where a local anesthetic is administered.

How Local Anesthetics are used :

- Local anesthesia are typically administered by dentists, surgeons, anaesthetists, general practitioners, and other doctors.
- Some medications containing a moderate local anesthetic are available on prescription or over the counter at pharmacies.
- Local anaesthetics can be administered as injections, creams, gels, sprays, or ointments, depending on their intended application.

Treating pain :

- Over-the-counter gels and sprays containing a local anesthetic can be used to alleviate minor pains like sore throats and mouth ulcers.
- Injections of a local anesthetic and steroid drug may be used to treat more serious problems, such as long-term joint discomfort.

Preventing pain during and after surgery :

- A local anaesthetic, usually given by injection, may be used along with a sedative medicine to keep you relaxed while an operation or procedure is carried out.
- Local anaesthetics are mainly used for relatively minor procedures, such as:
- A filling or wisdom tooth removal
- A minor skin operation, such as the removal of moles, warts and verrucas
- Some types of eye surgery, such as cataract removal
- A biopsy (where a sample of tissue is removed for closer examination under a microscope)
- A local anaesthetic may occasionally be used for more major surgery when it's important for you to be awake, such as during certain types of brain surgery, or to prevent pain after a major operation that's been carried out under a general anaesthetic.

The growing prevalence of pain in society, caused by an aging population and fast-paced lives, needs better pain treatment solutions. Pain can come from a variety of sources, including physical stress, mental challenges, and social constraints, thus judicious medication use is critical for effective therapy (Mills et al., 2019). Opioid analgesics, while very effective for pain relief, include considerable hazards such as addiction and serious health consequences, leading to abuse and associated public health challenges (Stayner & Copenhaver, 2012; Dowell et al., 2016).

Given these challenges, there is an increasing interest in local anesthetics (Las) as a safer pain control option. Las are largely used for acute and chronic pain management, but their effectiveness is restricted by their short duration of action, which typically ranges from 4 to 12 hours (Barletta & Reed, 2019). This limitation is especially problematic in postoperative

situations, where good pain management is important to recovery.

Current clinical practices, such as nerve blocks and catheter placements, frequently encounter complications such as catheter displacement, local hematoma, nerve injury, and local anesthetic toxicity, emphasizing the need for sustained-release formulations to improve the duration and reliability of analgesia (Jeng et al., 2010). This demand has prompted research into various drug delivery technologies, such as liposomes, microemulsions, and polymer-based carriers, with the goal of increasing pain management's reliability and safety (Joudeh & Linke, 2022).

One interesting development is the SABER-Bupivacaine formulation, which is a semi-viscous fluid containing 12% bupivacaine. This formulation is intended to provide extended analgesia after surgery, lowering reliance on opioids and improving recovery outcomes. Randomized controlled trials are being conducted to examine the efficacy and safety of this method for inguinal hernia repair.

Furthermore, recent advances in biomaterials have led to the investigation of chitosan and genipin as potential hydrogels for the regulated release of local anesthetics. These hydrogels are biocompatible and biodegradable, enabling for long-term medication administration. This could considerably improve postoperative pain management by lowering the frequency of injections and their accompanying side effects.The usual approach to postoperative pain management has evolved to multimodal techniques that include non-opioid analgesics like NSAIDs and acetaminophen, as well as local anesthetics. This technique attempts to reduce the negative effects of opioids, such as respiratory depression and reliance, while also improving pain control during the critical first 72 hours following surgery, when pain is often the most intense (Peccora & Zhou, 2015).

According to research, poorly managed acute postoperative pain can progress to chronic pain disorders, delaying recovery and raising healthcare expenses. Effective analgesia not only reduces patient stress but also allows for speedier movement, resulting in better surgical outcomes (Peccora & Zhou, 2015). Thus, the development of long-acting local anesthetics, such as HTX-011 (bupivacaine and meloxicam), holds promise for providing effective and long-lasting pain management in a variety of surgical settings.

In conclusion, the research emphasizes the critical need for novel delivery technologies and formulations that improve the efficacy and safety of local anesthetics. The development of sustained-release systems, such as CS-GP/PCL hydrogels, is a big step forward in pain management, seeking to prolong analgesic benefits while reducing potential problems. As research continues, the emphasis remains on optimizing pain control measures to enhance results in surgical and postoperative care, addressing both acute and chronic pain management.

Local anesthetics are of two tyes :

- Clinical Local anesthetic :

- amino amide Local anesthetic
- amino ester Local anesthetic

Chemical Structure :

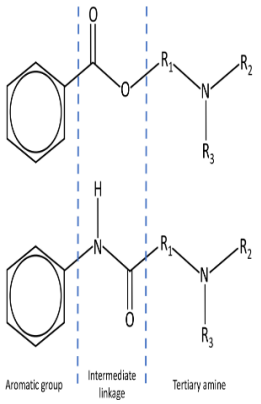

Fig.1 the structure of ester and amidelocal anestheics, each caintain an aromatic group, an intermediate linkage and tertiary amine

Local anesthetics are drugs that block pain in specific areas of the body. They have two main parts: a hydrophilic (water-loving) amine end and a lipophilic (fat-loving) aromatic end, connected by an intermediate chain. There are two types of local anesthetics: amino amides and amino esters.

Amino amides : (like lidocaine and bupivacaine) have an amide link and are metabolized in the liver. They are stable in solution and less likely to cause allergic reactions.

Amino esters: (like procaine and cocaine) have an ester link, are broken down in the plasma, are less stable, and have a higher chance of causing allergies.

A simple way to remember which drugs are amino amides is that they contain the letter "i" twice, just like "amino amides." Recent advancements include ropivacaine and levobupivacaine, which are designed to be safer and longer-lasting by using a specific form (S enantiomer) of the drug.

In 2011, the FDA approved liposomal bupivacaine (Exparel), which delivers bupivacaine in a special liposomal form for prolonged pain relief after surgery. This method reduces the need for opioids for up to 24 hours. In 2018, it was approved for use in nerve blocks.

However, studies have questioned whether liposomal bupivacaine is significantly better than regular bupivacaine. For example, a review found only minor, statistically significant differences in pain relief at 24 and 72 hours, but these differences may not be clinically meaningful.

Physiological activity :

The effectiveness of local anesthetics depends on several factors: their lipid solubility, how easily they spread through tissues, how well they bind to proteins, their ionization at body pH, and their ability to widen blood vessels (vasodilation).

1. Lipid Solubility: Local anesthetics that dissolve well in fats are more potent because nerve cell membranes are mostly made of fat. This means they can penetrate nerves faster and block sodium channels more effectively.

2. Diffusibility: How easily the anesthetic spreads through tissues affects how quickly it works.

3. Protein Binding: The stronger the anesthetic binds to proteins in the sodium channels, the longer it lasts.

4. Ionization: Local anesthetics can exist in two forms: ionized and non-ionized. The non-ionized form can pass through nerve

membranes and block sodium channels. The more non-ionized form present, the faster the anesthetic works. The ideal pH for most anesthetics is between 7.6 and 8.9, and when the pH of the tissue is closer to normal (7.35-7.45), the onset of action is quicker. If the pH drops (becomes more acidic), it favors the ionized form, slowing down the onset. This is why local anesthetics work slower in inflamed tissues. Adding sodium bicarbonate can help raise the pH and speed up the action, but too much can cause the anesthetic to clump together.

5. Vasodilation: Most local anesthetics (except cocaine) widen blood vessels, which can lead to faster absorption and shorter duration of action. To counteract this effect, epinephrine is often added to the anesthetic solution.

An in vitro study showed that amino amide local anesthetics, like bupivacaine and lidocaine, can affect the immune system by reducing the ability of certain white blood cells (granulocytes) to move effectively. Bupivacaine decreased their movement at higher concentrations, while lidocaine at lower concentrations actually increased their movement.

- Synthetic Local anesthetic :
- Cocaine derivatives

✓ Synthetic cocaine-derived LAs differ from cocaine because they have a much lower abuse potential and do not cause hypertension vasoconstriction (with few exceptions).

The suffix "-caine" at the ends of these medication names is derived from the word "cocaine", because cocaine was formerly used as a local anesthetic.

Examples

1. Short Duration of Action and Low Potency

1. Benzocaine
2. Procaine
3. Chloroprocaine

2. Medium Duration of Action and Medium Potency

1. Lidocaine
2. Prilocaine

3. High Duration and High Potency

1. Tetracaine
2. Bupivacaine
3. Cinchocaine
4. Ropivacaine

Advantages of local anesthesia :

1. Not inflammable.
2. Excellent muscle relaxant effect.
3. During local anesthesia the patient remains conscious.
4. It requires less skilled nursing care as compared to othes anesthesia like general anesthesia .
5. Maintain his own airway.

Disadvantages of local anesthesia :

1. There are individual variations in response to local anesthetic drugs.
2. Rapid absorption of the drug into the bloodstream can cause severe, potentially fatal reactions.
3. Apprehension may be increased by the patient's ability to see and hear. Some patients prefer to be unconscious and unaware

Properties of Local Anesthetics:

1) Not irritating to the tissue

2) No permanent alteration of nerve structure

3) Systemic toxicity should be low

4) Effective whether injected or applied topically

5) Time of onset of anesthesia should be as short as possible

6) Duration of action must be long enough to complete the procedure but not so long as to require an extended recovery

7) Should be stable in solution and easily biotransformed

8) Should not cause allergic reactions

9) Should be sterile or capable of being sterilized by use of heat

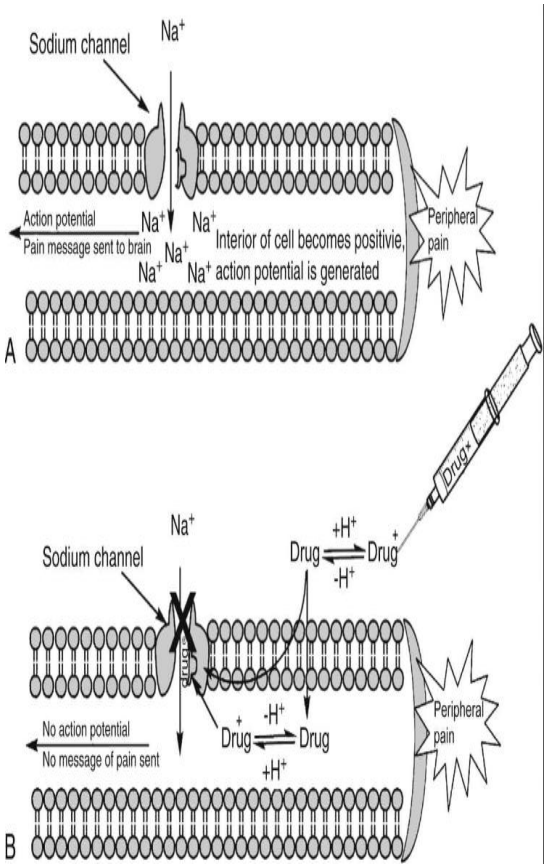

Fig.2 Mechanism of action of local anesthetic

- ***The mechanism of action :***

Local anesthetics produce anesthesia by inhibiting excitation of nerve endings or by blocking conduction in peripheral nerves. This is achieved by anesthetics reversibly binding to and inactivating sodium channels. Sodium influx through these channels is necessary for the depolarization of nerve cell membranes and subsequent propagation of impulses along the course of the nerve. When a nerve loses depolarization and capacity to propagate an impulse, the individual loses sensation in the area supplied by the nerve.

The order of affinity of local anesthetics for different sodium channel states is open is better than inactivated, which is better than resting. Thus, the open state of the sodium

channel is the primary target of local anesthetic molecules. The blocking of propagated action potentials is therefore a function of the frequency of depolarization. The mechanism for differential block, the block of pain perception without motor block, is still unclear.

Administration of Local Anesthetics :

When administering local anesthetics, several factors need to be considered for safety and effectiveness, including the patient's characteristics, the anesthetic dose, the use of epinephrine, the speed of injection, blood flow in the area, and the technique used.

1. Dose Calculation: Surgeons must calculate the maximum safe dose based on the patient's weight and medical history, especially regarding heart conditions. While anesthesiologists can help, the final responsibility for safe dosing lies with the surgeon.

2. Dilution: Local anesthetics often come in concentrations of 1% or 2%, which can be higher than needed. Diluting the anesthetic with sterile saline can lower the concentration, allowing for more volume without increasing the total dose.

3. Caution with Preparation: When preparing local anesthetics, it's crucial to ensure that the correct medications and doses are used. Mistakes can lead to serious issues, such as injecting the wrong substance.

4. Using Epinephrine: Adding epinephrine to the anesthetic can enhance safety and effectiveness. It helps slow down absorption, prolonging the anesthetic's action and improving control over bleeding during surgery. However, it should be used cautiously, especially in patients with heart issues or high blood pressure.

5. Bicarbonate Addition: Adding bicarbonate to the solution can reduce the burning sensation patients feel during injection, improving comfort.

6. Injection Technique: Speed matters; injecting too quickly can increase toxicity. It's better to inject slowly and sequentially across different sites to maintain lower peak levels in the bloodstream. Areas with high blood supply, like the face and scalp, require even slower injections.

7. Aspirating Before Injection: Always aspirate (pull back on the syringe) before injecting to avoid injecting directly into a blood vessel, which can cause rapid increases in drug levels and possible adverse reactions.

8. Choosing Needles: Using smaller needles can reduce pain. Warming the anesthetic solution and injecting slowly can also help minimize discomfort.

9. Combining Anesthetics: Sometimes, surgeons mix different local anesthetics to benefit from their unique properties, such as combining a short-acting anesthetic with a long-acting one for extended pain relief. However, caution is needed with specific formulations like liposomal bupivacaine, as mixing can lead to overdose risks.

DOSAGES OF LOCAL ANESTHETICS :

DRUG	ONSET	MAXIMUM DOSE (WITH EPINEPHRINE)	DURATION (WITH EPINEPHRINE)
Lidocaine	Rapid	4.5mg/kg(7mg/kg)	120 min(240 min)
Mepivacaine	Rapid	5mg/kg(7 mg/kg)	180 min(360 min)
Bupivacaine Ropivacaine Levobupivacaine	Slow Medium Medium	2.5mg/kg(3mg/kg) 2-3mg/kg 2.0mg/kg or 400mg in 24 hrs	4 hrs (8 h) 3 hrs (6 h) 4 to 6 hrs (8-12 h)
Procaine	Slow	8mg/kg(10 mg/kg)	45 min (90 min)
Chloroprocaine	Rapid	10mg/kg(15 mg/kg)	30 min (90 min)
Etidocaine	Rapid	2.5mg/kg(4mg/kg)	4 hrs (8 h)
Prilocaine	Medium	5mg/kg(7.5mg/kg)	90 min(360 min)
Tetracaine	Slow	1.5mg/kg(2.5mg/kg)	3 hrs (10 h)

Drug Profile :

1. **Bupivacaine :**

Chemical formula : C18H28N2O.

Molecular weight : 288.43g/mol.

Mechanism of action :

Local anesthetics (LAs) work by stopping nerves from sending pain signals to the brain. They do this by blocking sodium (Na+) channels, which are necessary for nerve cells to generate electrical signals. When these channels are blocked, nerves can't send impulses, and sensation in the area is lost. Local anesthetics have three main parts: an aromatic ring, a middle part (either an ester or amide), and an amine group. Two key chemical properties affect how they work:

1. Lipid solubility: This determines how strong the anesthetic is, how long it lasts, and how much it binds to proteins in the blood.

2. pKa (ionization constant): Anesthetics with a lower pKa work faster because they have more uncharged molecules, which can easily pass through the nerve membrane and block the sodium channels.

Nerve fibers that carry pain signals (small, fast-firing fibers) are blocked more easily than larger fibers, which carry motor signals. This is why low doses of local anesthetics can block pain without affecting movement.

In the heart and other tissues, sodium channels play a role in maintaining electrical activity. Local anesthetics, especially bupivacaine, can affect the heart by slowing down pacemaker activity and potentially causing dangerous heart rhythms at high doses. Bupivacaine can also be more resistant to standard treatments for heart toxicity due to how it interacts with other cell receptors.

In the central nervous system, local anesthetics can first cause excitement and then lead to depression, affecting the brain's normal function.

Different types of nerves are affected by LAs at different rates. Smaller nerves, like pain fibers, are blocked more easily because they have shorter distances between the nodes (gaps along the nerve), while larger nerves, like motor nerves, take longer to block completely.

Administration :

Bupivacaine comes in three concentrations: 0.25%, 0.5%, and 0.75%. It can be used for various procedures, including:

1. Local infiltration for post-surgical pain relief.
2. Peripheral nerve blocks for dental or minor surgeries.
3. Spinal anesthesia for major surgeries or cesarean deliveries.
4. Epidural anesthesia for labor pain.
5. Caudal blocks for surgeries below the umbilicus, often in children.

To make the effects of bupivacaine last longer, doctors often add other medications. For example:

1. Alpha-2 agonists like clonidine or dexmedetomidine can significantly extend anesthesia duration.
2. Dexamethasone may also help prolong effects, though it's unclear how it works.
3. Magnesium can enhance the duration of local anesthetics as well.

Research is ongoing to find more ways to safely extend the effectiveness of local anesthetics.

In recent years, using ultrasound guidance for nerve blocks has reduced the risk of local anesthetic toxicity. By visualizing the nerves, doctors can avoid injecting into blood vessels and recognize any issues early, helping to prevent high levels of bupivacaine in the bloodstream.

Advers effect :

1. Dose Variation:

Depends on the procedure, tissue vascularity, area, depth/duration needed, and patient health.

2. Drug Interactions:

Can interact with migraine medications, blood thinners, antidepressants, and monoamine oxidase inhibitors.

3. Allergic Reactions:

1. Rare for preservative-free amide anesthetics.
2. More common with ester anesthetics or preservatives like methylparaben.
3. Epinephrine reactions can be misidentified as allergies.

4. Methemoglobinemia:

1. Typically linked to benzocaine or prilocaine, but rare cases with bupivacaine exist.
2. Low levels (1%-3%) may be asymptomatic; higher levels (10%-40%) can cause symptoms like cyanosis and difficulty breathing.

5. Common Side Effects:

1. Nausea and vomiting.
2. Chills or shivering.

3. Headaches and back pain.
4. Dizziness, anxiety, and restlessness.
5. Blurry vision and tinnitus.

Toxicity :
Local Anesthetic Toxicity (LAST)

1. Toxicity Levels:
Local anesthetics can cause similar symptoms, but bupivacaine is particularly cardiotoxic.
The risk of toxicity is rare, occurring in about 1 in 1,000 to 1 in 10,000 cases.

2. Administration Sites:
The risk of toxicity varies by injection site, with intravenous administration being the highest risk.

Commonly more toxic sites (most to least):

1. Intravenous
2. Intercostal
3. Caudal
4. Epidural
5. Abdominal wall blocks
6. Sciatic and brachial plexus blocks.

3. Causes of Toxicity:
Most cases occur due to accidental injection into a blood vessel or rapid absorption.
Rarely, patients may show toxicity at lower doses due to l-carnitine deficiency.

5. Signs and Symptoms:

1. Neurological:
Early signs include tingling, tinnitus, blurry vision, and drowsiness.
Late signs can include agitation, confusion, seizures, and coma.

2. Cardiovascular:
Early signs like hypertension and tachycardia can progress to severe hypotension, irregular heartbeats, and cardiac arrest.

Treatment of Bupivacaine Toxicity :

1. Initial Management:
Supportive care, including CPR and airway management.
Seizures may be treated with quick-acting medications like midazolam.

2. Lipid Emulsion Therapy:

Landmark research showed that lipid emulsion can effectively treat bupivacaine toxicity. It acts as a "rescue" treatment and has become a first-line option.

Dosing recommendations:

For patients over 70 kg: Bolus 100 mL rapidly, then infuse 200-250 mL.
For patients under 70 kg: Bolus 1.5 mL/kg, then infuse 0.25 mL/kg/min.

3. Consider Cardiopulmonary Bypass: This may be needed if other treatments fail.

Bupivacaine is a local anesthetic that can be formulated to provide sustained pain relief:

HYR-PB21: A sustained-release formulation of bupivacaine that can provide pain relief for up to 72 hours after a procedure.

Liposomal bupivacaine: An aqueous suspension of multivesicular liposomes that can provide long-lasting pain relief for up to 72 hours. It's used in a variety of surgeries, including hemorrhoidectomy, bunionectomy, and inguinal hernia repair.

SABER-bupivacaine: A depot formulation of bupivacaine that's designed to be injected surgically to achieve long-term pain relief.

HTX-011: An investigational extended-release local anesthetic formulation that contains bupivacaine and low-dose meloxicam. It can provide sustained pain relief for up to 3 days.

Bupivacaine is a commonly used analgesic that's four times more potent than lidocaine. It's often used to reduce pain after surgery, such as after the extraction of impacted third molars. However, bupivacaine can be cardiotoxic, so it should be used with caution in patients taking certain medications.

2.Mepivacaine :

Chemical formula : C15H22N2O

Molecular weight : 246.348

Drug profile :

Absorbed locally. The rate of systemic absorption of local anesthetics is dependent upon the total dose and concentration of drug administered, the route of administration, the vascularity of the administration site, and the presence or absence of epinephrine in the anesthetic solution.

Mepivacaine is approximately 75% bound to plasma proteins. Generally, the lower the plasma concentration of drug, the higher the percentage of drug bound to plasma. Rapidly metabolized, with only a small percentage of the anesthetic (5 percent to 10 percent) being excreted unchanged in the urine. The liver is the principal site of metabolism, with over 50% of the administered dose being excreted into the bile as metabolites.

It is rapidly metabolized, with only a small percentage of the anesthetic (5 percent to 10 percent) being excreted unchanged in the urine.The liver is the principal site of metabolism, with over 50% of the administered dose being excreted into the bile as metabolites. The half-life of mepivacaine in adults is 1.9 to 3.2 hours and in neonates 8.7 to 9 hours. The mean seizure dosage of mepivacaine in rhesus monkeys was found to be 18.8 mg/kg with mean arterial plasma concentration of 24.4 µg/mL. The intravenous and subcutaneous LD 50 in mice is 23 mg/kg to 35 mg/kg and 280 mg/kg respectively.

Mechanism of action :

Local anesthetics stop nerves from sending signals by making it harder for them to get excited, slowing down how quickly the signals travel, and reducing the strength of the signals. How quickly nerves lose function depends on their size, whether they have a protective myelin layer, and how fast they normally send signals. In simple terms, when local anesthetics are used, the order in which sensations are lost is:

1. Pain

2. Temperature

3. Touch

4. Awareness of body position (proprioception)

5. Muscle control and movement

This explains why, during procedures, you might first lose the ability to feel pain, and then gradually lose other sensations and muscle control.

Side effects of mepivacaine :

1. Anxiety, feeling restless or excited.
2. Depression, dizziness.
3. Tremors.
4. Blurred vision, ringing in your ears.

3.Lidocaine :

Chemical formula : C14H22N2O
Molecular weight : 234.3373

Drug profile :

Lidocaine :

Lidocaine is a local anesthetic commonly used to numb areas of the body during medical procedures. It works by blocking nerve signals, effectively preventing pain.

Common Uses:

1. Local or regional anesthesia for surgeries
2. Treating arrhythmias (irregular heartbeats)
3. Relief for conditions like anal fissures and back pain

How It Works:
Lidocaine blocks sodium channels in nerve cells, stopping them from sending pain signals to the brain. This process leads to numbness in the treated area.

Forms Available:
Lidocaine comes in various forms, including injections, creams, gels, and patches, under brand names like Xylocaine, Emla, and Lidoderm.

Pharmacology:
Absorption: Quickly absorbed from mucous membranes; oral intake has low effectiveness due to first-pass metabolism.
Distribution: Widely distributed in the body, especially in well-perfused tissues like muscle.

Metabolism: Mainly processed in the liver; metabolites are excreted through the kidneys.

Half-life: Typically lasts 1.5 to 2 hours in the body.

Safety and Side Effects: Lidocaine is generally safe but can cause side effects such as dizziness, numbness, and, in rare cases, serious heart issues if overdosed. Caution is advised for pregnant or nursing women.
Lidocaine is a local anesthetic that works by blocking nerve signals to provide pain relief in specific areas of the body. Here's how it functions:

Mechanism of Action:
Lidocaine stabilizes nerve membranes by preventing sodium ions from moving in and out. It enters nerve cells as an uncharged molecule, becomes charged, and then attaches to sodium channels inside the cells. This blockage stops the nerves from sending pain signals to the brain.

2. Effects on Nerves:
By preventing nerve depolarization, lidocaine stops pain signals before they can even start. This means it not only stops pain from traveling to the brain but also stops the pain from being generated.

3. Impact on Other Systems:
Besides its effects on nerves, lidocaine can also impact the central nervous system (CNS) and the heart. Initially, it may stimulate the CNS but can lead to depression afterward. In the heart, lidocaine reduces how easily heart cells can activate, which slows down heart rhythms and decreases heart contractions.
In simple terms, lidocaine is effective at numbing pain by blocking nerve signals and can also affect the heart and brain.

A slow-release lidocaine sheet (SRLS) with PLGA was also able to produce a sustained effect for 1 week without inducing inflammation of the sciatic nerve in a rat model (51). It was also reported that lidocaine gel containing diethylene glycol had about a 3.89-fold increase in analgesic activity (52).

Literature Review:
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2. William G. Brockmann, DDS, PhD
3. Taylor Bourn and Sister Michaela Serpa
4. Wentao Deng, Yu Yan, Peipei Zhuang, Xiaoxu Liu, Ke Tian, Wenfang Huang & Cai Li

Conclusion :

The article discusses various local anesthetic delivery systems, highlighting their characteristics, clinical applications, and shortcomings. Despite advancements in sustained-release formulations for pain management, including FDA-approved products like Exparel™ and Zynrelef™, clinical challenges remain.
Recent innovations, such as infrared-controlled nanoparticles and thermosensitive hydrogels, show promise but lack FDA approval. The article emphasizes the need for safer long-acting anesthetics, as current options like bupivacaine can pose risks, especially in sensitive populations like children.

Novel formulations, including SABER-Bupivacaine and BPV-loaded hydrogels, demonstrate potential for prolonged pain relief with fewer side effects. However, more research is needed to ensure their efficacy and safety.

Overall, the future of local anesthetics may lie in new chemical entities and advanced drug delivery systems that provide effective pain management while minimizing toxicity.

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