Perioperative Lignocaine

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KEY POINTS

- Lignocaine is an amide local anaesthetic and class 1b antiarrhythmic.
- It has analgesic, antiarrhythmic, antinociceptive, anti-inflammatory, and immune-modulating properties.
- It can be used in the management of acute perioperative pain and chronic neuropathic pain.
- Enhanced recovery after surgery protocols recommend intravenous lignocaine as an opioid-sparing multimodal analgesic adjunct.
- Immune modulatory properties of lignocaine may be beneficial in patients with cancer.

INTRODUCTION

Lignocaine is one of the most popular and widely used drugs in anaesthesia practice. It was discovered in the 1940s by Nils Lofgren and Bengt Lundquist, was introduced under the name Xylocaine in 1942, and was first approved for clinical use in Sweden in 1948.[1] It is an amide local anaesthetic used for topical, infiltration, and intravenous regional analgesia, central neuraxial block, peripheral nerve block, systemic intravenous infusion for acute postoperative pain, and dental anaesthesia. Lignocaine belongs to class 1b of the Vaughan–William classification of antiarrhythmics. It is a versatile drug due to its application in the field of anaesthesia, pain management, and cardiovascular diseases. The multifaceted effects on pain control are mediated via its analgesic, antihyperalgesic, and anti-inflammatory properties. This makes it a favourable option for perioperative analgesia.

This tutorial aims to explore the mechanism of action of lignocaine, its potential uses in the perioperative setting, and its safety profile and adverse effects.

LIGNOCAINE

Structure

Lignocaine is a monocarboxylic acid amide with the molecular formula $C_{14}H_{22}N_2O$. It is a white crystalline powder formed by the condensation of *N*,*N*-diethylglycine and 2,6-dimethylaniline. The chemical structure consists of an aliphatic chain linked to an aromatic ring and an amine group (Figure).[2]

Mechanism of Action and Pharmacodynamics

Local anaesthetics act primarily by blocking voltage-gated sodium channels on the neuronal membrane.[4] Voltage-gated sodium channels are complex transmembrane proteins consisting of α and β subunits. The predominant binding site for the local

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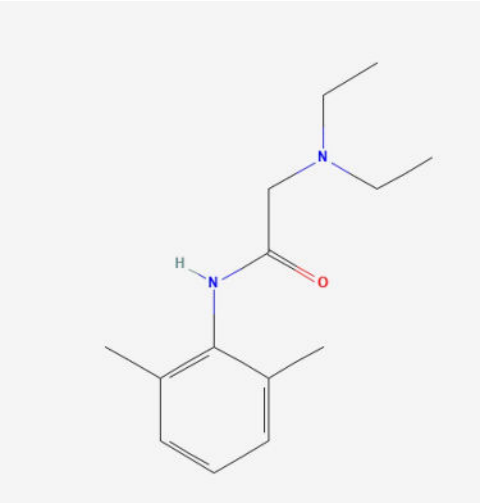

Figure. Structure of lignocaine (open access).[3]

anaesthetic is the α subunit located on the inner surface (intracytoplasmic) part of the cell membrane. Under physiological conditions, the sodium channel exists in 3 states: resting, open (activated), or inactivated. Local anaesthetics have increased affinity for the open or inactivated channel state.

When administered, the un-ionized, lipid-soluble form of the local anaesthetic diffuses across the phospholipid neuronal membrane. In the axoplasm, the local anaesthetic becomes partly ionized while a proportion remains un-ionized. The ionized form becomes trapped in the cell cytoplasm and binds reversibly and in a concentration-dependent manner with the open and inactivated sodium channels from within. This prevents further depolarization of the nerve by blocking the influx of sodium ions through these channels.[5]

Each local anaesthetic has slightly different pharmacodynamics in terms of onset, potency, and duration, owing to the different properties of each molecule. The speed of onset of the local anaesthetic depends on its pK_a, which will dictate the ratio of ionized and un-ionized moieties at a given pH. The potency and duration of action depend on the molecule's lipid solubility and protein binding, respectively. These properties specific to lignocaine are listed in Table 1.

Pharmacokinetics

Absorption and Distribution

Lignocaine is 60 to 80% protein bound, mainly to α-1-glycoprotein. It readily crosses the blood–brain barrier and placenta through simple passive diffusion and is also excreted in breast milk. Lignocaine has a distribution half-life of 5 to 8 minutes, passing first through highly perfused areas like the heart, lung, and liver and then to less perfused areas like muscle and adipose tissue.[6] The volume of distribution ranges from 0.7 to 1.5 L/kg. It can exist in both ionized and un-ionized forms, with 25% remaining un-ionized at a physiological pH of 7.4, owing to its pK_a of 7.8.[2]

Metabolism and Excretion

With a high hepatic extraction ratio of 70%, the metabolism of lignocaine is dependent primarily on the amount of liver blood flow rather than the liver's metabolic capacity. Therefore, an adequate liver blood flow is pivotal for the efficient metabolism of lignocaine.

Pharmacodynamic Variable	Lignocaine	Bupivacaine
pK_a (ratio of ionized and un-ionized moieties at a given pH)	7.8	8.1
Lipid solubility (hydrophobicity: octanol/buffer partition coefficient)	366	3420
Protein binding	60 to 80%	95%
Relative conduction blocking potency	2 (intermediate potency)	8 (high potency)
Duration of action	30 to 120 minutes (moderate duration)	180 to 240 minutes (long duration)

Table 1. Factors Affecting Pharmacodynamics of Lignocaine. The data are presented along with those of bupivacaine for comparison[5]

The main metabolic pathway for lignocaine is oxidative *N*-dealkylation (90%) to an active metabolite monoethylglycinexylidide, which gets further de-ethylated to glycinexylidide. The latter gets further hydrolysed and oxidized to give the main metabolic byproduct 4-hydroxy-xylidine, which is excreted in the urine.[6] This transformation is dependent on the cytochrome P450 system (CYP3A4 and CYP1A2) present in the liver.[7] Inhibition of the cytochrome P450 system by drug interaction with enzyme inhibitors will decrease lignocaine clearance by 20% and increase the plasma concentration of monoethylglycinexylidide. This metabolic pathway has been used clinically to assess liver function by measuring the monoethylglycinexylidide concentration after lignocaine administration.

Lignocaine and its metabolites undergo renal excretion, with only 10% excreted unchanged in urine. The elimination half-life of lignocaine ranges from 90 to 120 minutes in healthy individuals. This is prolonged in patients with hepatic dysfunction, renal impairment, or congestive cardiac failure.[8] Plasma levels decrease rapidly after discontinuation of a prolonged infusion. The context-sensitive half-life of lignocaine after a 3-day infusion is 20 to 40 minutes.[9]

Clinical Effects

Th clinical properties of lignocaine are dependent on the blockade of voltage-gated open and inactivated sodium channels. It also acts on potassium, calcium, 5-hydroxytryptamine, Gα_q-coupled and *N*-methyl-D-aspartate receptors. The interaction between lignocaine and multiple receptors leads to variety of clinical effects (Table 2).[6]

Adverse Effects

Use of intravenous lignocaine for pain control has been associated with adverse effects, most notably light-headedness, dizziness, drowsiness, visual disturbances, metallic taste, or tinnitus.[10] Blunting of the airway reactivity can lead to delayed emergence in some cases, possibly due to patients' ability to better tolerate the presence of an airway. The use of lignocaine can also be associated with type 1 hypersensitivity reactions.

Lignocaine has a narrow therapeutic index from 2.5 to 3.5 μg/mL. Through action on sodium and potassium channels, local anaesthetics can produce systemic toxicity by blocking impulse generation in the cardiovascular and central nervous systems. Early symptoms of systemic toxicity are metallic taste, perioral numbness, blurred vision, dizziness, tinnitus, and paresthesia of the tongue. Severe toxic levels can lead to agitation, seizures, atrioventricular heart block, arrhythmia, and cardiac arrest. Signs of neurotoxicity begin at plasma concentrations above 5 μg/mL, with cardiotoxicity seen at levels above 10 μg/mL.[9] The signs and symptoms of systemic toxicity are often potentiated by physiological derangements like hypoxia, hypercarbia, and acidosis. It is prudent to check an electrocardiogram for the presence of any arrhythmias before commencing lignocaine as an infusion and monitor for arrythmia carefully during infusion.

Relative Contraindications for Lignocaine Infusion

Although lignocaine infusion is well tolerated in most patients, due to its narrow therapeutic index, it is important to keep contraindications for its use in mind. Lignocaine is relatively contraindicated in patients with significant heart disease, neurological disorders, allergy to the drug, and severe renal or hepatic impairment (Table 3).[10]

USES OF PERIOPERATIVE LIGNOCAINE

Acute Perioperative Pain Management

Systemic administration of lignocaine infusion has been used perioperatively as an analgesic adjunct for multimodal analgesia. Most of the trials have been conducted in laparoscopic or open abdominal procedures. Intravenous lignocaine given as a 0 to

Clinical Effect	Description
Analgesic, antihyperalgesic, and antinociceptive	Reduces inputs from injured peripheral nerves and spinal cord neurons and suppresses secondary hyperalgesia by preventing peripheral and central sensitization
Antiarrhythmic	Class 1b: decreases the slope of phase 4 of the action potential, resulting in decreased action potential length and duration of the refractory period of Purkinje fibres Slight negative chronotropic effect
Anti-inflammatory	Inhibits leukocyte activation and adhesion to the site of injury Suppression of release of surgical stress response-induced proinflammatory cytokines, like interleukin-6, interleukin-8, and C-reactive protein
Immunomodulatory	Induction of apoptosis, reduction of tumour cell migration, diminished surgical stress response, preserved immunocompetence, and anti-inflammatory effects may have antineoplastic effects and possibly reduce recurrence of metastatic cancer
Antithrombotic	Inhibit platelet aggregation
Antimicrobial	Inhibit growth of Gram-positive and Gram-negative *Mycobacterium* and various fungi

Table 2. Clinical Effects of Lignocaine[6]

Contraindication	Details
Significant heart disease	Second- or third-degree heart block
	Congestive heart failure
	History of Adam-Stokes syndrome
	Wolff-Parkinson White syndrome
	Concurrent treatment with class 1 antiarrhythmics
	Use of amiodarone
Neurological disorder	History of uncontrolled seizure
Others	Sensitivity or allergy to lignocaine
	Severe hepatic impairment
	Severe renal impairment
	Acute porphyria
	Electrolyte imbalance

Table 3. Relative Contraindications for Lignocaine Infusion

1.5 mg/kg bolus followed by an infusion of 1.5 to 3 mg/kg/h has improved postoperative pain scores in patients undergoing laparoscopic major abdominal surgery. The effect was observed for 24 hours after surgery, with decreased pain scores at rest and on movement. There was an associated decrease in the consumption of postoperative opioids, decreased nausea, and decreased time to first flatus.[11] Therefore, for patients in which epidural anaesthesia is contraindicated or not desired, an intravenous infusion of lignocaine can be used as an opioid-sparing analgesic. Intravenous lignocaine infusions have also been used in nonabdominal surgeries where it has shown to decrease postoperative pain and opioid consumption and facilitate early recovery.[12]

Chronic Pain Management

Lignocaine is used clinically for the management of chronic pain. It appears to prevent the transmission of nerve impulses through the blockade of sodium channels, thereby reducing input from nociceptors. Some preclinical studies also support the anti-inflammatory mode of action and potential central blockade of NMDA receptors, although at doses much higher than those used in humans. However, evidence supporting lignocaine efficacy for chronic pain management is limited.[13] It has been used to treat chronic neuropathic pain and prevent the development of chronic postsurgical pain after breast and thoracic surgery.[14–16]

Transdermal patches of 5% lignocaine have been used for treating localized and superficial neuropathic pain. When applied to intact painful skin, it relives pain caused by damaged nerves and is well tolerated without plasma levels reaching toxic levels.[17]

Regional Analgesia

Lignocaine has been used in central neuraxial and peripheral nerve blocks to provide perioperative analgesia. 1% to 2% solutions are used for regional nerve blocks, including epidural anaesthesia. Lignocaine's onset of action is rapid (5 to 15 minutes), and the duration of block depends on the dose given, concentration used, targeted nerves, and status of the patient. The duration of action may last up to 60 minutes without epinephrine, 120 minutes with epinephrine for infiltration anaesthesia, and 120 to 240 minutes when administered for a peripheral nerve block.[4] Three millilitres of lignocaine (1.5%) along with epinephrine (1:200 000 [45 mg lignocaine and 15 μg epinephrine]) is used as an epidural test dose to rule out intrathecal or intravascular catheter placement.[18]

Antiarrhythmic and Cardiopulmonary Resuscitation

Lignocaine is a class 1b antiarrhythmic used for the management of ventricular arrhythmias. Lignocaine has been recommended in the management of shockable rhythms (ventricular fibrillation or pulseless ventricular tachycardia) in doses of 1 to 1.5 mg/kg as a first dose and 0.5 to 0.75 mg/kg as a second dose as an alternative to amiodarone in the American Heart Association's adult advanced life support guidelines.[19] However, the European and Australian resuscitation societies (ILCOR and ANZCOR) have categorized the level of evidence as low/weak and have de-emphasized the use of lignocaine in their algorithms.

Minimize Sympathetic Response to Airway Manipulation

Use of intravenous lignocaine in the doses of 1.5 to 2 mg/kg 2 to 3 minutes before laryngoscopy and intubation as well as extubation attenuates the sympathetic response by blunting the increase in heart rate, systolic blood pressure, mean arterial pressure, and catecholamine release.[20]

Laryngospasm Prevention

Lignocaine can be administered intravenously or topically to the larynx within 5 minutes of tracheal extubation to prevent laryngospasm in children during anaesthesia.[21]

Suppressing Fentanyl-Induced Cough

Intravenous lignocaine (0.5 mg/kg) given 1 minute before fentanyl can be used to suppress cough associated with fentanyl administration.[22]

Preventing or Reducing Pain Associated with Propofol Injection

One of the disadvantages of using propofol as an induction agent is the distressing pain associated with its administration. Lignocaine mixed with propofol or as an intravenous pretreatment with or without venous occlusion is effective in preventing propofol injection pain.[23]

Improving Postoperative Recovery with Mention in Enhanced Recovery after Surgery Protocols

Use of intravenous lignocaine has shown to decrease the intensity of postoperative pain and reduce opioid consumption. The opioid-sparing effect, along with attenuated surgical stress response, leads to early return of bowel function with reduced incidence of postoperative nausea and vomiting. Systemic lignocaine has been shown to shorten the duration of postoperative ileus by 8 hours and decrease the incidence of postoperative nausea and vomiting by 10 to 20%.[24] These factors contribute to the early and enhanced recovery after surgery, thus decreasing the overall length of hospital stay. However, clinicians should be aware of the recommendations on the efficacy and safety of using intravenous lignocaine.[25]

Opioid-Free Anaesthesia

The potential side effects of opioids in the perioperative period have encouraged the use of opioid-sparing techniques for pain management. Intravenous lignocaine is one option that can be used as an opioid-sparing adjunct as a part of an opioid-free anaesthesia regimen, along with regional blocks to enhance patient recovery.[26]

Preventing Recurrence of Cancer

Recent research is exploring the effects of intravenous lignocaine on improving cancer outcomes. Due to the induction of apoptosis, reduction of tumour cell migration, diminished surgical stress response, preserved immunocompetence, and anti-inflammatory effects, lignocaine may have antineoplastic effects. Use as an agent to reduce the recurrence rates of metastatic cancer is currently under investigation.[27]

SUMMARY

In the perioperative setting, intravenous lignocaine has an important role as an analgesic and antiarrhythmic. Its use is associated with improved patient-reported outcome measures. It is now a part of various practice guidelines, but hesitation may still exist over its use due to yet to be proven efficacy in some areas and to its narrow therapeutic index.

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