INTERNATIONAL JOURNAL OF CURRENT ADVANCED RESEARCH
ISSN: O: 2319-6475, ISSN: P: 2319-6505, Impact Factor: 6.614
Available Online at www.journalijcar.org
Volume 13; Issue 03; March 2024; Page No.2920-2923
DOI: http://dx.doi.org/10.24327/ijcar.2024.2923.1637

Review Article

EVALUATION OF BUPIVACAINE IN ORAL AND MAXILLOFACIAL SURGERY: A REVIEW

Paras Doshi*[1] , Sheeraz Badal[2], Punam Nagargoje[3], Dnyaneshwar Sakare[4], and Shreyas Dungarwal[5]

Department of Oral and Maxillofacial Surgery, MIDSR Dental College, Latur, Maharashtra, India

A R T I C L E I N F O

Article History:
Received 12th February, 2023
Received in revised form 26th February, 2024
Accepted 14th March, 2024
Published online 28th March, 2024

Key words:

Bupivacaine hydrochloride, Marcaine, Local anesthesia, Oral surgery, Pharmacodynamics

A B S T R A C T

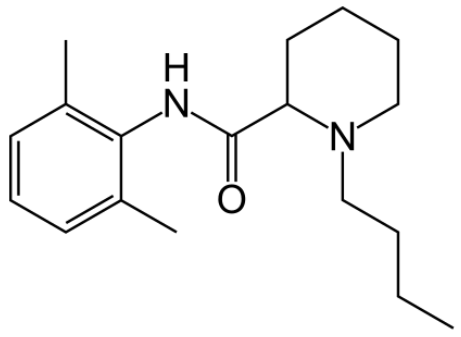
A review of significant current literature concerning bupivacaine hydrochloride (Marcaine) is presented with particular emphasis on clinical use in oral surgery. The major advantages compared with other presently used local anaesthetics are an increased duration of action and a favourable potency-to-toxicity ratio. Bupivacaine HCL (1-butyl-2', 6' pipecoloxylidide hydrochloride)* is a long-acting amide local anaesthetic (Fig. 1). First synthesised in 1957 by Ekernstam at A. B. Bafors Laboratories in Molndel, Sweden, this drug has undergone trials and received varying degrees of acceptance. Bupivacaine is a potent local anaesthetic with unique characteristics in the amide group of local anaesthetics. Local anaesthetics are used in regional anaesthesia, epidural anaesthesia, spinal anaesthesia, and local infiltration. Local anaesthetics generally block the generation of the action potential in nerve cells by increasing the threshold for electrical excitation. This activity reviews the mechanism of action, adverse event profile, toxicity, dosing, pharmacodynamics, and monitoring of bupivacaine.

INTRODUCTION

Aim

- Outline the indications for the use of bupivacaine.
- Review the mechanism of action of bupivacaine.
- Explain the contraindications to using bupivacaine.

Summarise interprofessional team strategies for improving care coordination and communication to advance pain control and improve outcomes when using bupivacaine.



Bupivacaine HCL (1-butyl-2', 6' pipecoloxylidide hydrochloride)

Indications

Bupivacaine is a potent local anaesthetic with unique characteristics in the amide group of local anaesthetics, first discovered in 1957. Local anaesthetics are used in regional anaesthesia, epidural anaesthesia, spinal anaesthesia, and local infiltration. Local anaesthetics generally block the generation of an action potential in nerve cells by increasing the threshold for electrical excitation. The progression of anaesthesia is dependent on factors such as the diameter, degree of myelination, and conduction velocity of nerve fibres. In clinical practise, the order of loss of nerve function is as follows.[1] [2]

- Pain
- Temperature
- Touch
- Proprioception
- Skeletal muscle tone

Indications **Mechanism of Action**

All local anaesthetics contain three structural components: an aromatic ring, a connecting group that is either an ester (procaine) or an amide (bupivacaine), and an ionizable amine group. In addition, all LAs have two chemical properties that determine their activity:

- Lipid solubility
- Ionisation constant (pKa)

Lipid solubility determines the potency, duration of action, and plasma-protein binding of local anaesthetics. Local anaesthetics enter nerve fibres as a neutral-free base. Ionised forms and the cationic form block conduction by their interaction on the inner surface of the Na+ channel. Moreover,

Corresponding author:* **Paras Doshi
Department of Oral and Maxillofacial Surgery, MIDSR Dental College, Latur, Maharashtra, India.

LAs with a lower pKa have a more rapid onset of action, meaning more of it exists in an uncharged form, which renders faster diffusion to the cytoplasmic side of the Na+ channel. Na+ channels are membrane proteins that propagate action potentials in axons, dendrites, and muscle tissue. They initiate and maintain membrane potential in specialised heart and brain cells. Depending on the tissue Na+ level, channels contain one larger alpha subunit and one or two smaller beta subunits. The alpha subunit, the site of ion conduction, and local anaesthetic binding have four similar domains, each with six alpha-helical membrane-spanning segments. The external surface of the alpha-subunit is heavily glycosylated, which allows the channel to orient properly within the cytoplasmic membrane. In contrast to local anaesthetics, scorpion toxins and tetrodotoxin have binding sites on the extracellular surface of the Na+ channel.

Conduction of nerve impulses occurs through the generation of an action potential along an axon; local anaesthesia results when LAs bind the Na+ channel and inhibit the Na+ permeability necessary for the action potential. Local anaesthetics selectively inhibit the open form of voltage-gated Na+ channels. Na+ channel blockade results in the decrease or elimination of conduction in vascular smooth muscle, leading to relaxation. In the heart, this leads to decreased pacemaker activity and prolongation of the refractory period. This action is unique to bupivacaine due to its decreased rate of dissociation from blocked sodium channels, which leads to a prolongation of the maximal rate of depolarization (Vmax) and the potential for ventricular arrhythmias. Also, LAs produce dose-dependent myocardial depression and interference with Ca2+ signalling within the cardiac muscle because they also bind and inhibit cardiac voltage-gated Ca2+ and K+ channels. Local anaesthetics also bind beta-adrenergic receptors and inhibit epinephrine-stimulated cAMP formation, which can explain the refractoriness of bupivacaine CV toxicity to standard resuscitation guidelines. In the central nervous system (CNS), local anaesthetics may cause increased excitability, followed by depression. Neuronal tissues have different susceptibilities to local anaesthetics. Depolarizing currents in nerves move along nodes of Ranvier, and 2 to 3 nodes must be blocked to impair neuronal conduction completely. Smaller fibres have smaller internodal distances and, therefore, get blocked by local anaesthetics more quickly. [3]

Administration

Bupivacaine is offered in three different concentrations: 0.25%, 0.5%, and 0.75%.

Administration is by local infiltration (post-surgical analgesia), peripheral nerve blocks (dental or other minor surgical procedures, orthopaedic surgery), spinal anaesthesia (injected into the CSF to produce anaesthesia for orthopaedic surgery, abdominal surgery, or caesarean delivery), epidural anaesthesia or analgesia for labour pain, and a caudal block (anaesthesia and analgesia below the umbilicus, usually for paediatric surgery). [4] Adjuvants are often added to local anaesthetics for nerve blocks to prolong the anaesthetic effects compared to LA alone. Alpha-2 agonists such as clonidine or dexmedetomidine combined with LA have been shown to significantly increase the duration of anaesthesia. Additionally, dexamethasone, when mixed with the local anaesthetic for nerve blocks, has also been shown to increase the duration of anaesthesia, although the mechanism is unclear as to whether it is a direct neural effect or simply the systemic effect of the steroid anti-inflammatory processes. With its N-methyl D-aspartate receptor antagonist effects, magnesium has also been associated with a prolonged duration of action of local anaesthetics for nerve blocks. Studies are ongoing evaluating the effects of these and other potential adjuvants on LAs to prolong effectiveness while minimising the risk of toxicity.[5]

In the last decade, it has been shown that ultrasound-guided nerve blocks are associated with a decreased risk of local anaesthetic toxicity. Presumably, visualisation of the nerve and surrounding structures decreases the likelihood of injection into a vascular structure and increases the early recognition of this occurrence, thereby lessening the possibility of reaching toxic levels of bupivacaine in the bloodstream.[6]

Use in Oral Surgery

Attempts to use the increased duration of action of bupivacaine to modify post-operative oral surgical pain have been made. Rapid onset, profound surgical anaesthesia, lack of toxic reactions, and increased duration of action have been realised. With the exception of Hellden and Associates, 28 studies have shown a significant delay in the initial request for post-operative analgesia. Laskin and Associates describe a protracted period of post-operative analgesia persisting after normal sensation has returned. Local anaesthetic agents in the perioral area are subject to a decreased duration of action due to the vascularity of the area. Nevertheless, obtundation of post-operative oral surgical pain for up to twelve hours is reported. Feldman and Norderam's" original oral surgical statistics indicated no difference in duration of action between 0.25% and 0.5% bupivacaine. More recent oral surgical studies indicate that the onset, duration, and degree of surgical anaesthesia are enhanced by increasing drug concentrations. Studies comparing bupivacaine with and without vasoconstrictors demonstrate no significant differences in duration between these groups. Prolongation of bupivacaine block in oral surgery may be achieved by combination with low molecular weight dextran-40. In one study, the mean duration of post-operative analgesia in the bupivacaine-dextran group was 36 hours compared to 12 hours for the bupivacaine-saline control. The mechanism suggested is the formation of a dextran-bupivacaine complex, which is absorbed much more slowly than bupivacaine alone.

Adverse Effects

The dose of bupivacaine depends on the procedure, the vascularity of the tissue, the area, the number of segments blocked, the depth or duration of anaesthesia needed, and the patient's physical condition. Bupivacaine may interact with ergot medications used for migraine headaches, blood thinners, antidepressants, or monoamine oxidase inhibitors. Immunologic reactions to local anaesthetics are rare. Allergic reactions to preservative-free amide-type local anaesthetics are rare and usually not reported. A true anaphylactic response appears more common with ester local anaesthetics or preservatives; epinephrine-containing local anaesthetic reactions are often misdiagnosed as allergic reactions. Patients may also react to preservatives such as methylparaben, which are included with local anaesthetics. Methemoglobinemia is typically associated with benzocaine or prilocaine; however,

case reports exist implicating bupivacaine in rare instances. At low levels (1% to 3%), methemoglobinemia can be asymptomatic, but higher concentrations (10% to 40%) may accompany cyanosis, cutaneous discoloration (grey), tachypnea, dyspnea, exercise intolerance, fatigue, dizziness, syncope, and weakness. Some more common adverse effects include nausea, vomiting, chills or shivering, headache, back pain, dizziness, sexual dysfunction, restlessness, anxiety, vertigo, tinnitus, blurry vision, and tremors, which may precede more severe adverse effects such as convulsions, myoclonic jerks, coma, and cardiovascular collapse[2].

Contraindications

Contraindications include hypersensitivity to the drug or its components, hypersensitivity to amide anesthetics, infection at the injection site, obstetric paracervical block, obstetricanesthesia using 0.75% concentration, intravenous regional anesthesia, and intra-articular continuous infusion. Clinicians should exercise caution in patients with hypersensitivity to sulfites, liver impairment (the liver clears amides), kidney impairment, impaired cardiac function, heart block, hypovolemia, hypotension, and elderly, debilitated, or acutely ill patients.[7]

Monitoring

Standard monitoring required during the administration of bupivacaine includes

- Continuous EKG
- SpO2
- Blood pressure

Ask patients to report any numbness around the lips or mouth, a metallic taste, ringing in their ears, tremors, or ominous feelings. If the patient reports any of these symptoms, the administration of bupivacaine must stop immediately, and treatment as per guidelines must follow.[2]

Toxicity

Most local anaesthetics produce similar signs and symptoms, but the ratio of neurotoxicity to cardiotoxicity may differ, with bupivacaine being the most cardiotoxic. The incidence of toxicity is rare: 1 to 1000 to 1 to 10000. Be concerned for local anaesthetic toxicity (LAST) with abnormal cardiovascular or neurological signs and symptoms. The site of administration of local anaesthetics also influences the risk of toxicity. Unintended direct intravenous injection or rapid vascular uptake of the drug is the most common reason for bupivacaine toxicity, which has an upper limit of 2.5 to 3.5 mg/kg. Depending on the vascularity of the injection site and the technique, toxicity of the medication can occur if administered at the upper limit of the dosing recommendations. Signs and symptoms of toxicity may occur rapidly or be delayed. Rarely, patients exhibit toxicity to bupivacaine at doses much lower than the suggested upper limits of dosing. This toxicity appears to be due to a rare condition related to l-carnitine deficiency. Patients affected may exhibit cardiac toxicity at doses as low as 1.1 mg/kg of bupivacaine injected cutaneously. Case reports exist describing these cases of low-dose toxicity in patients later discovered to be deficient in l-carnitine. A rat study demonstrated this model and found that the administration of supplemental l-carnitine could reverse this effect.[8]

Most-to-least toxic sites

Intravenous>Intercostal>Caudal>Epidural>Interfascial plane blocks of the abdominal wall (TAP)>Psoas compartment blocks>Sciatic blocks>Cervical plexus block>Brachial plexus block

Pathophysiology

At therapeutic levels, local anaesthetics block voltage-gated Na-channels at the alpha subunit inside the channel, preventing Na+ influx, depolarization, and action potential generation. They affect cardiac Na+ channels and neurons in the brain at toxic levels, blocking K+, Ca2+, and NMDA receptors. Local anaesthetics also interfere with cellular processes, including oxidative phosphorylation, free fatty acid utilisation, and cAMP production. Toxic levels of local anaesthetics in the heart lead to conduction irregularities, impaired cardiac contractility, and the loss of vascular tone secondary to extreme vasodilation.

Treatment

Treatment of bupivacaine toxicity has long been challenging due to its profound neurologic and cardiac toxicity. Previously, treatment had been supportive, with standard cardiopulmonary resuscitation, airway management, and seizure control with quick-acting GABA agonists such as midazolam. Because of the long duration of action of bupivacaine, toxicity was especially problematic. In centres where cardiopulmonary bypass was readily available, it was used to support the toxic patient until the drug was adequately metabolised and cleared, which may take hours. In the early 2000s, landmark research by Guy Weinberg revealed that lipid emulsion, such as the type that serves as the carrier for total parenteral nutrition formulations, was effective in rescuing laboratory animals from bupivacaine toxicity. The profound results in animals (mice and dogs) led to several case reports where lipid emulsion was used as a last resort in human patients with profound cardiovascular collapse following nerve blocks with long-acting local anaesthetics such as bupivacaine and ropivacaine. Over the following 15 years, the treatment with lipid emulsion became widely accepted as effective, was adopted by the American Society of Regional Anaesthesia as the standard for treating local anaesthetic systemic toxicity (LAST), and has been adopted into their treatment algorithm. Once only used as a last-resort treatment, it is now widely used as a first-line treatment for these patients. Facilities that administer local anaesthetics should have lipid emulsions readily available for emergencies. Interestingly, high-dose epinephrine has shown associations with decreased effectiveness of lipid emulsions in the treatment of LAST. This evidence further emphasises the importance of early treatment with lipid emulsion when LAST is suspected. Detailed treatment algorithms are available through the American Society of Regional Anaesthesia's website. [9] The current dosing recommendations for 20% lipid emulsion are as follows:

For a patient greater than 70 kg, bolus 100 mL of lipid emulsion 20% rapidly over 2 to 3 minutes and then infuse 200 to 250 mL over the next 15 to 20 minutes. Redosing may be necessary up to a maximum dose of 12 mL/kg.

For a patient of less than 70 kg, bolus 1.5 mL/kg lipid emulsion 20% rapidly over 2 to 3 minutes, followed by an

infusion of 0.25 mL/kg/min for ideal body weight to an upper limit of 12 mL/kg.

A cardiopulmonary bypass should also still be considered early in cases where other treatments are ineffective.

Enhancing Healthcare Team Outcomes

Bupivacaine is administered to patients by many healthcare professionals, including the surgeon, anesthesiologist, pain specialist, emergency department physician, and nurse practitioner. However, all interprofessional healthcare team members involved in administering and dispensing the drug must know its potential side effects and toxicity. Resuscitative equipment must be in the room at the time of the injection, and surgical nurses must be familiar with the proper use of this equipment in an emergency. The most common reason for a complication is an injection of the drug into the artery or vein, which can result in adverse cardiac and CNS effects. [10] [11] Pharmacists can be involved in preparing the agents and verifying proper dosing and administration, working with the anesthesiologist or nurse anaesthetist. They can also assist in cases of toxicity with the drugs needed to address toxic states. Bupivacaine use requires an interprofessional team approach, including physicians, specialists, specialty-trained nurses, and pharmacists, all collaborating across disciplines to achieve optimal patient results. [Level 5]

References

1. Shah, J., Votta-Velis, E. G., & Borgeat, A. (2018). New local anaesthetics. Best Practice & Research. Clinical Anaesthesiology, 32(2), 179–185. PMID: 30322458
2. Wolfe, R. C., & Spillars, A. (2018). Local Anaesthetic Systemic Toxicity: Reviewing Updates From the American Society of Regional Anaesthesia and Pain Medicine Practise Advisory. Journal of PeriAnesthesia Nursing, 33(6), 1000–1055. PMID: 30449428
3. Li, J., Duan, R., Zhang, Y., Zhao, X., Cheng, Y., Chen, Y., Yuan, J., Li, H., Zhang, J., Chu, L., Xia, D., & Zhao, S. (2018). Beta-adrenergic activation induces cardiac collapse by aggravating cardiomyocyte contractile dysfunction in bupivacaine intoxication. PLoS One, 13(10), e0203602. PMID: 30273351
4. Iskander, A., & Gan, T. J. (2018). Novel analgesics in ambulatory surgical patients. Current Opinion in Anaesthesiology, 31(6), 685–692. PMID: 30346316
5. Prabhakar, A., Lambert, T., Kaye, R. J., Gaignard, S. M., Ragusa, J., Wheat, S., Moll, V., Cornett, E. M., Urman, R. D., & Kaye, A. D. (2019). Adjuvants in clinical regional anaesthesia practise: a comprehensive review. Best Practice & Research. Clinical Anaesthesiology, 33(4), 415–423. PMID: 31791560
6. Barrington, M. J., & Uda, Y. (2018). Did ultrasound fulfil the promise of safety in regional anaesthesia? Current Opinion in Anaesthesiology, 31(5), 649–655. PMID: 30004951
7. Petrikas, A. Zh., Ol'khovskaia, E. B., Medvedev, D. V., & Diubalo, M. V. (2013). Disputable issues in Malamed's "Handbook of Local Anaesthesia" (2004). Stomatologiia (Mosk), 92(2), 71–76. PMID: 23715461
8. Wong, G. K., Pehora, C., & Crawford, M. W. (2017). L-carnitine reduces susceptibility to bupivacaine-induced cardiotoxicity: an experimental study in rats. Canadian Journal of Anaesthesia, 64(3), 270–279. PMID: 28032304
9. Neal, J. M., Woodward, C. M., & Harrison, T. K. (2018). The American Society of Regional Anaesthesia and Pain Medicine Checklist for Managing Local Anaesthetic Systemic Toxicity: 2017 Version. Regional Anesthesia and Pain Medicine, 43(2), 150–153. PMID: 29356775
10. Teunkens, A., Vermeulen, K., Peters, M., Fieuws, S., Van de Velde, M., & Rex, S. (2019). Bupivacaine infiltration in children for postoperative analgesia after tonsillectomy: a randomized controlled trial. European Journal of Anaesthesiology, 36(3), 206–214. PMID: 30640245
11. Hussain, N., McCartney, C. J. L., Neal, J. M., Chippor, J., Banfield, L., & Abdallah, F. W. (2018). Local anaesthetic-induced myotoxicity in regional anaesthesia: a systematic review and empirical analysis. British Journal of Anaesthesia, 121(4), 822–841. PMID: 30236244

How to cite this article:

Paras Doshi, Sheeraz Badal, Punam Nagargoje, Dnyaneshwar Sakare, and Shreyas Dungarwal.(2024). Evaluation of Bupivacaine in Oral and Maxillofacial Surgery: A Review. *International Journal of Current Advanced Research.*13(03), pp.2920-2923.

****