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Intravenous Regional Anesthesia: Pharmacology, Adjuvants, Complications, and Management of Local Anesthetic Systemic Toxicity

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Abstract:

Background: Intravenous regional anesthesia (IVRA), commonly known as Bier block, is a simple and effective technique for short surgical procedures on the extremities. Despite its advantages, the technique carries risks related to tourniquet use, local anesthetic systemic toxicity (LAST), inadequate analgesia, and adverse drug effects. This review summarizes the recognition and management of LAST and examines the pharmacology, clinical use, safety, and limitations of local anesthetics and adjuvants used in IVRA. Management of LAST depends on early identification, airway and oxygenation support, seizure control, appropriate cardiovascular resuscitation, and prompt administration of 20% lipid emulsion. Lidocaine and prilocaine remain the principal IVRA agents because of their rapid onset and acceptable safety profiles, whereas mepivacaine, ropivacaine, chloroprocaine, and articaine have more limited roles. Adjuvants including dexmedetomidine, dexamethasone, ketamine, opioids, and nonsteroidal anti-inflammatory drugs may improve block quality, reduce tourniquet pain, or prolong postoperative analgesia, but each introduces specific adverse effects and contraindications. Careful patient selection, correct dosing, reliable tourniquet technique, continuous monitoring, and immediate access to resuscitation equipment are essential. The review also emphasizes practical prevention strategies and balanced selection of agents according to procedure duration and patient risk. Adherence to these principles can improve efficacy while minimizing preventable complications associated with IVRA.

Keywords: IVRA; LAST; Lidocaine; Dexmedetomidine; Lipid-emulsion.

Introduction:

The management of LAST is based on three main pillars: seizure control, advanced cardiac life support (ACLS), and prompt administration of a 20% lipid emulsion. In patients who are hemodynamically stable with isolated seizures, intravenous benzodiazepines are considered first-line therapy. Small doses of propofol may be used as an alternative for seizure control; however, it should be used cautiously as it may worsen cardiovascular instability. All patients should receive supplemental oxygen, while those with apnea, malignant arrhythmias, or cardiac arrest require immediate airway management and full resuscitative measures. The main goals are to ensure adequate oxygenation, maintain organ perfusion, and prevent worsening acidosis until lipid therapy is initiated **(1).**

Before lipid therapy was introduced, management relied mainly on ACLS and sometimes cardiopulmonary bypass, although its availability is limited. Vasopressors were used but were found to potentially worsen acidosis and arrhythmias. The concept of lipid therapy emerged from experimental studies showing that lipid emulsions can reduce

the active free fraction of lipophilic drugs. This led to the development of the lipid sink and lipid shuttle theories, where lipid emulsion binds lipophilic local anesthetics and reduces their toxicity while enhancing redistribution and clearance. Additionally, lipid therapy has a direct cardiotonic effect, improving myocardial function beyond simple drug sequestration. Although generally safe, lipid emulsion therapy may cause mild adverse effects such as laboratory interference, bronchospasm, or gastrointestinal symptoms. Serious complications are rare and mainly associated with prolonged or excessive use. Importantly, propofol is not a substitute for lipid emulsion therapy due to insufficient lipid content and potential cardiovascular depression. Early administration of lipid therapy significantly improves outcomes and reduces the need for vasopressors. If intravenous access is not available, intraosseous administration can be used as an alternative **(2).**

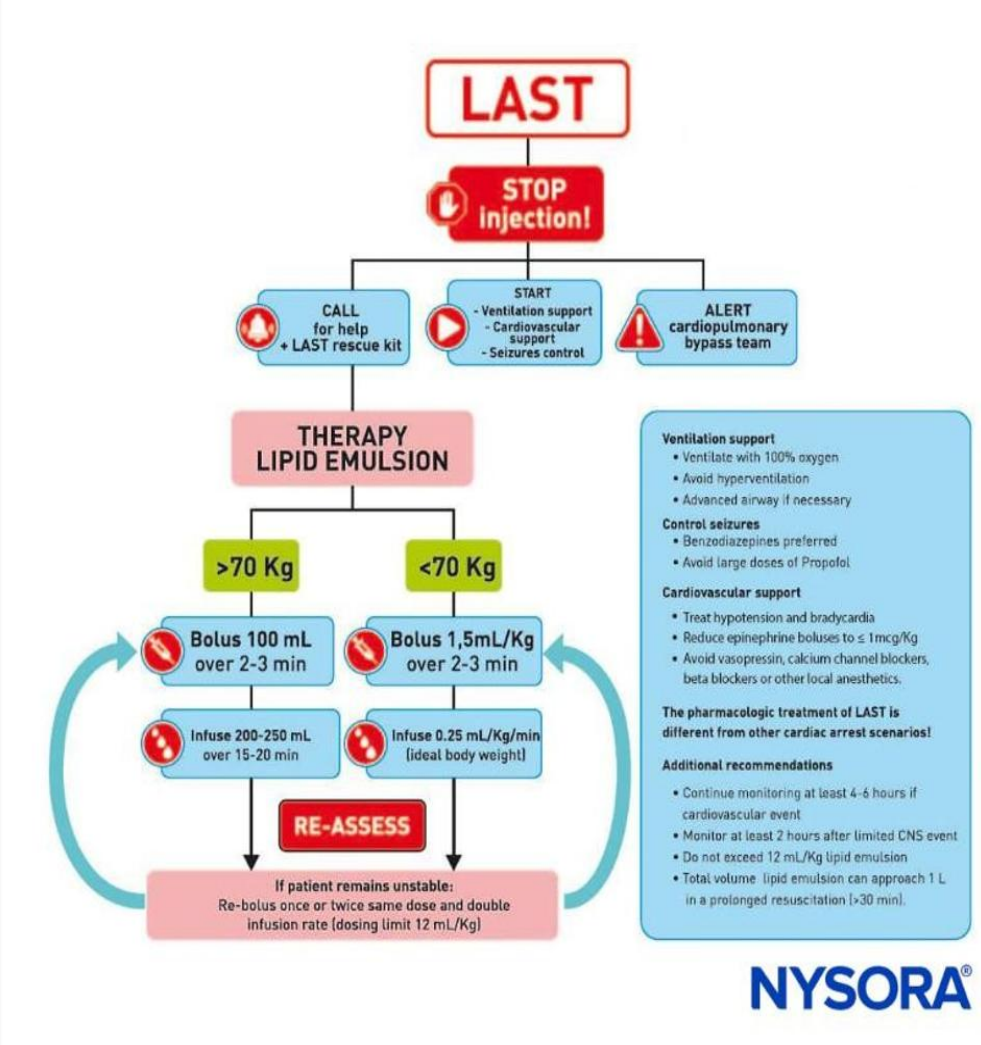

Fig. 1: Management of LAST **(2)**

- **Equipment (tourniquet)-related complications**

Equipment-related complications are mainly associated with the pneumatic tourniquet and technical aspects of the IVRA procedure. Tourniquet malfunction, cuff leakage, inadvertent deflation, or failure to completely isolate the limb circulation may permit local anesthetic escape into the systemic circulation, increasing the risk of toxicity. Tourniquet pain is one of the most common complications, especially during prolonged procedures or when a double-

cuff pneumatic tourniquet is not used. Sustained tourniquet inflation may also produce ischemic pain, discomfort, and systemic hypertension **(3).**

Rare neurologic complications including injury to the median, ulnar, and musculocutaneous nerves have been reported. These injuries are believed to result from prolonged direct pressure exerted by the tourniquet on peripheral nerves, producing changes similar to crush injuries. Therefore, tourniquet inflation time should generally not exceed 2 hours **(4).** Compartment syndrome is another rare but serious complication, particularly during lower-limb IVRA for fracture reduction. It may result from incomplete limb exsanguination combined with injection of large anesthetic volumes into the isolated extremity **(4).** Minor complications associated with IVRA include skin discoloration, petechiae, urticaria, thrombophlebitis, and pain during injection **(5).**

Pharmacology of Local anesthetics used in IVRA

There are many local anesthetic choices for IVRA **(Table 1).** The most commonly used anesthetics are lidocaine and prilocaine. Potent local anesthetics are not commonly used as there is a risk of a sudden release of a large volume of local anesthetic into the systemic circulation **(6).**

Table 1: Comparison between several local anesthetics used in IVRA (7):

Drug	Dose	Comment
Lidocaine	3 mg/kg 40 ml 0.5%	Most commonly used in the USA. Some cardiac arrest and death have been reported following IVRA
Prilocaine	3 mg/kg 40 ml 0.5%	Less systemic toxicity than lidocaine. No reports of cardiac arrest Methemoglobinemia may occur with doses over 600 mg
Mepivacaine	5 mg/kg	Reported better intraoperative conditions than lidocaine
Ropivacaine	40 ml 0.2–0.25% (25 ml 0.375% with forearm tourniquet)	Longer postoperative analgesia than lidocaine
Chloroprocaine	40 ml 0.5%	Urticaria/venous irritation Solutions containing preservative have been associated with thrombophlebitis
Articaine	40 ml 0.5%	Rapid onset, rapid metabolism Skin rashes/urticaria common Not available preservative free in the USA

Preservatives in anesthetics are associated with venous irritation and allergic reactions, and therefore preservative-free formulations are preferred **(8).**

1. Lidocaine

Lidocaine, formerly also referred to as lignocaine, is an amide local anesthetic agent. Lidocaine is a well-known local anesthetic that has found wide use as a local topical anesthetic and as an acute intervention for ventricular arrhythmias. Intravenous infusion of lidocaine has seen increasing use as a treatment of chronic pain. Moreover, the

intra- or immediately post-operative systemic administration of lidocaine has been used to decrease the need for other post-operative analgesics, particularly opioids **(9).**

Lidocaine remains the first-line agent in North America. It is widely used because of its rapid onset (approx. 4.5 minutes) and predictable offset (approx. 5.8 minutes) after tourniquet release. It has a well-established safety record, particularly due to its antiarrhythmic properties. The recommended dose is 40 mL of 0.5% lidocaine, without epinephrine. Despite being slightly more potent in analgesia than prilocaine, lidocaine is associated with a slightly higher systemic toxicity profile **(10).**

Lidocaine Structure

Lidocaine is an amide type local anesthetic. Chemically, it is 2-(Diethylamino)-N-(2,6-dimethylphenyl) acetamide hydrochloride as shown in Figure 2 **(11)**.

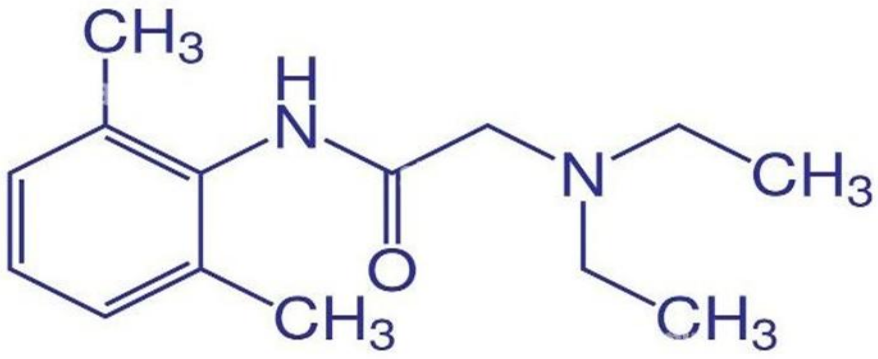

Figure (2): Structure of Lidocaine **(11)**

Mechanism of Action

Lidocaine, like other local anesthetics, acts on sodium ion channels within nerve cell membranes. The uncharged form diffuses through neural sheaths and ionizes in the axoplasm. The resulting cation binds to sodium channels from the inside, preventing nerve depolarization. Lidocaine is moderately protein-bound (65%) and has a medium duration of action. It is less lipid-soluble compared to other agents, limiting its potency. Its volume of distribution is 0.7 to 1.5 L/kg, and it is metabolized in the liver **(12).**

Lidocaine's weak base nature (pKa 7.7) means about 25% of molecules are un-ionized at physiological pH, allowing for a rapid onset of action. However, efficacy can decrease in inflamed tissues due to reduced un-ionized lidocaine, increased blood flow, and inflammatory mediators affecting sodium channels **(9).**

It stabilizes the neuronal membrane by inhibiting the ionic fluxes required for the initiation and conduction of impulses, thereby effecting local anesthetic action **(11).**

Administration

Various routes of administration utilize different preparations of lidocaine. It includes the following: **(12)**

- Very dilute concentrations, in the order of 0.05 to 0.1%, can be infiltrated subcutaneously in large volumes to provide tumescent local anesthesia, resulting in swelling and firmness of the site, which may be beneficial for certain surgical procedures.
- Dilute solutions of 0.25 to 0.5% are used for intravenous regional anesthesia (Bier's block) or infiltration into subcutaneous tissue.

- 1 to 2% solutions are used for regional nerve blocks, including epidural anesthesia, and are also available in intravenous preparations for antiarrhythmic use.
- 1 to 2% aqueous gels, typically including an antiseptic such as chlorhexidine, are used to topicalize and lubricate the urethra prior to procedures like Foley catheterization.
- 4% solution is used for topical anesthesia of the mucous membranes of the airway, including the mouth, pharynx, and respiratory tract, either by gargling, spraying, or using an atomizer.
- 5% ointment, typically mixed with hydrocortisone, is employed topically on other mucous membranes such as the skin or in the rectum.
- 10% solution is also used topically for airway anesthesia, typically by spraying from a metered-dose atomizer.

The aqueous preparations from 0.5 to 2% are available in either plain forms or with 1 per 200000 epinephrine (dentistry sometimes uses versions with 1 per 100000 epinephrine or more) and are available with or without preservatives. Other products include medicated plasters impregnated with lidocaine, intended to treat chronic postherpetic neuralgia. Lidocaine and prilocaine are available premixed in a eutectic 5% cream (containing 2.5%) which is often used to anesthetize small areas of skin prior to procedures. Doses used for infiltrative or regional anesthesia will depend on the specific block **(9).**

Adverse Effects

Most side effects occur when plasma concentrations rise to toxic levels. The drug reaches the intravascular compartment most rapidly when administered into the intercostal space, followed by the caudal, epidural, brachial plexus, femoral and subcutaneous spaces. The maximum safe dose by body weight may be taken to be 3 mg/kg, or 7 mg/kg when using preparations with epinephrine, although the literature quotes various other doses. Smaller amounts can still result in side effects and toxicity if given intravascularly. Lidocaine is thought to be more neurotoxic than other local anesthetics, especially when high concentrations are applied directly to nervous tissue. Use of highly concentrated lidocaine (2.5 to 5%) for spinal anesthesia correlates with a greater incidence of transient radicular irritation syndrome, which is a self-limiting painful condition affecting the calves, thighs, and buttocks **(13, 14).**

Contraindications

The drug is contraindicated in patients with a known severe adverse reaction. Anaphylactic reactions to lidocaine are possible but rare. Methemoglobinemia can occur due to lidocaine metabolism to O-toluidine. This metabolite is more likely to be present when very high doses are given, but it may also occur with lower doses where the patient is taking other medications that can precipitate methemoglobinemia or where the patient has a hemoglobinopathy or another cause of anemia. Lidocaine preparations containing epinephrine cause demonstrable cardiovascular effects even if only given in small amounts, and it is prudent for essential hemodynamic monitoring to be carried out before and during use solutions containing vasopressors, particularly if there is any specific concern over the patient's cardiovascular status **(15).**

Prilocaine

Prilocaine, also known as propitocaine, is an amide-type local anesthetic widely used in regional anesthesia, particularly in intravenous regional anesthesia (IVRA). It is widely considered the preferred LA in Europe due to its excellent balance of potency and low toxicity. It is metabolized in the liver and generally well-tolerated. While 0.75% prilocaine may be used under experienced supervision, 0.5% is generally recommended. A notable concern is the risk of methemoglobinemia, which led to its withdrawal from the North American market. However, analysis of 45,000 IVRA cases found no serious adverse events or fatalities, confirming its excellent safety profile when dosed appropriately **(16).**

Prilocaine Structure

Prilocaine is an amide-type local anesthetic and chemically described as N-(2-methylphenyl)-2-(propylamino) propanamide hydrochloride. It differs structurally from lidocaine in that it is a secondary amine rather than a tertiary amine, a feature that contributes to its lower toxicity profile as shown in figure 3 **(17)**.

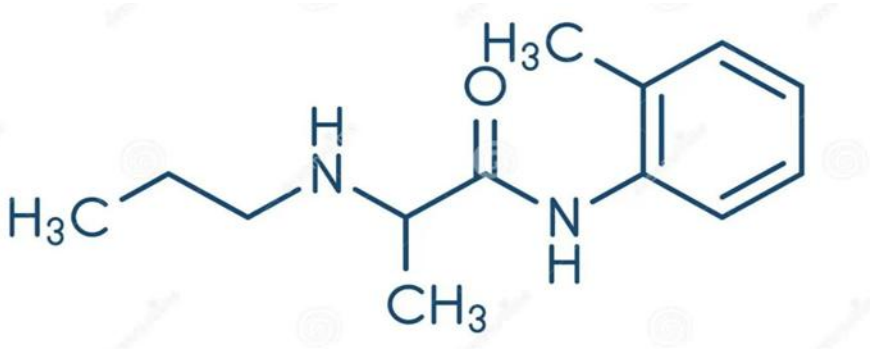

Figure (3): Structure of Prilocaine **(17)**

Mechanism of Action

Prilocaine acts by blocking voltage-gated sodium channels in nerve cell membranes. The uncharged form of the drug diffuses across the neural membrane and becomes ionized within the axoplasm. The ionized form then binds to intracellular sodium channels, preventing depolarization and propagation of nerve impulses. This results in reversible loss of sensation in the affected area. Prilocaine has moderate protein binding and a relatively large volume of distribution. It also demonstrates the highest clearance among amide local anesthetics, which contributes to its lower plasma concentration and reduced systemic toxicity. Its physicochemical properties allow for efficient tissue penetration and rapid onset of anesthesia. Like other amide anesthetics, it stabilizes neuronal membranes by inhibiting ionic fluxes required for nerve impulse initiation and conduction **(18).**

Administration

Prilocaine is administered via several routes depending on the clinical indication **(19):**

- Dilute solutions (0.5%) are commonly used for intravenous regional anesthesia (Bier's block).
- Higher concentrations may be used for infiltration and peripheral nerve blocks.

It is also available in combination with lidocaine as a eutectic mixture (EMLA cream) for topical anesthesia of intact skin prior to minor procedures **(20).**

Adverse Effects

Most adverse effects of prilocaine are dose-dependent and occur when plasma concentrations reach toxic levels. Compared to lidocaine, prilocaine has a lower risk of central nervous system and cardiovascular toxicity. However, a unique and clinically significant adverse effect is Methemoglobinemia, which results from its metabolism to o-toluidine. This metabolite oxidizes hemoglobin to methemoglobin, reducing its oxygen-carrying capacity. Clinically significant methemoglobinemia is rare and usually occurs with high doses (typically exceeding 600 mg) or in susceptible individuals such as those with anemia or enzymatic deficiencies **(21).**

Contraindications

Prilocaine is contraindicated in patients with known hypersensitivity to amide local anesthetics. It should be used with caution in patients at increased risk of methemoglobinemia, including those with anemia, cardiorespiratory

compromise, or concomitant use of oxidizing drugs **(14).**

Mepivacaine

Mepivacaine is an amide-type local anesthetic with intermediate onset and duration, commonly used in regional anesthesia **(22).**

Structure of Mepivacaine

Mepivacaine is an amide-type local anesthetic chemically designated as 1-methyl-2',6'-pipecoloxylidide hydrochloride. It consists of a lipophilic aromatic ring linked to a hydrophilic tertiary amine through an amide bond as shown in **figure 4.** This amide linkage confers greater chemical stability and a longer duration of action compared with ester local anesthetics. Mepivacaine has moderate lipid solubility and a pKa of approximately 7.6, allowing a relatively rapid onset of action due to a higher proportion of the non-ionized form at physiological pH **(23)**.

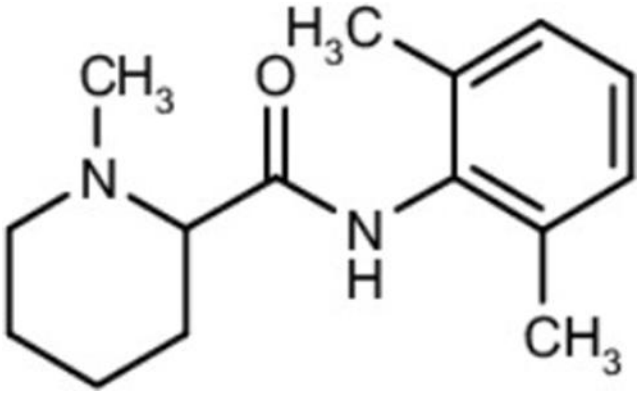

Figure (4): Structure of Mepivacaine **(23)**

Mechanism of action

Mepivacaine reversibly blocks voltage-gated sodium channels (Nav channels) on neuronal cell membranes. By preventing sodium influx during membrane depolarization, it inhibits the initiation and propagation of action potentials, resulting in reversible loss of sensory and, at higher concentrations, motor nerve conduction. Small myelinated and unmyelinated nerve fibers are more susceptible than larger motor fibers. Compared with lidocaine, mepivacaine produces less vasodilation, contributing to a slightly longer duration of anesthesia without the routine need for a vasoconstrictor **(24)**.

It can be used for infiltration, nerve blocks, and occasionally IVRA. However, it is less commonly used in IVRA compared to lidocaine and prilocaine. Systemic toxicity (CNS and cardiovascular) may occur at high plasma levels. Compared to prilocaine, it has a higher risk of accumulation due to slower metabolism. It's contraindicated in patients with hypersensitivity to amide anesthetics. Caution is required in hepatic impairment due to liver metabolism **(25).**

Ropivacaine

Ropivacaine is a long-acting amide local anesthetic and the pure S(-)enantiomer, developed to reduce the cardiotoxicity associated with bupivacaine. Ropivacaine is structurally similar to bupivacaine but less lipophilic, which contributes to its improved safety profile. It blocks sodium channels in nerve fibers, with a degree of sensory–motor differentiation favoring sensory block, which is beneficial for postoperative analgesia. Although not routinely used in IVRA, studies suggest that concentrations such as 0.2–0.25% may improve tourniquet tolerance and prolong postoperative analgesia. It carries a lower cardiotoxicity compared to bupivacaine, but toxicity may still occur at high doses. It should be avoided in patients with severe cardiac conduction disorders or known hypersensitivity **(5).**

Chloroprocaine

Chloroprocaine is an ester-type local anesthetic characterized by very rapid onset and short duration of action. It is an ester-linked anesthetic rapidly hydrolyzed by plasma cholinesterases, leading to short systemic exposure. Like other local anesthetics, it blocks sodium channels, preventing nerve impulse transmission. Its rapid onset makes it useful for short procedures; however, its very short duration limits its role in IVRA. It my cause low systemic toxicity due to rapid metabolism, but allergic reactions may occur more commonly than with amide agents. It's contraindicated in patients with pseudocholinesterase deficiency or known ester allergy **(26).**

Articaine

Articaine is a unique amide local anesthetic containing an ester group, widely used in dental anesthesia. Articaine contains both amide and ester components, allowing partial metabolism in plasma in addition to hepatic metabolism. It blocks sodium channels similarly to other local anesthetics but has enhanced tissue penetration due to its thiophene ring. Primarily used in dental procedures; its role in IVRA is limited but has been explored in some studies. It's generally well tolerated, though rare cases of nerve injury (particularly in dental use) have been reported. However, it's contraindicated in patients with hypersensitivity to local anesthetics or sulfite-containing preparations **(27).**

Dosing Guidelines

There is currently no universal consensus on the exact volume or concentration of LAs for IVRA. However, commonly accepted practices suggest **(28):**

- 1 mL/kg body weight for upper limbs.
- 1.5 mL/kg for lower limbs.
- Alternatively, fixed volumes of 40–50 mL for upper extremities and 60–80 mL for lower extremities are frequently used.

It is well documented that higher concentrations of LAs result in faster onset and better motor blockade, but care must be taken to balance this with toxicity risks **(29).**

An ideal anesthetic for IVRA would offer **(30):**

- High potency with low systemic toxicity,
- Rapid onset and offset,
- Hemodynamic stability,
- Minimal tourniquet pain,
- Prolonged post-deflation analgesia.

Adjuvants used with local anesthetics

Adjuvants are commonly added to local anesthetic agents during intravenous regional anesthesia (IVRA) to improve the quality and duration of anesthesia and postoperative analgesia. These agents may accelerate the onset of sensory and motor block, decrease tourniquet pain, prolong postoperative pain relief, and reduce the requirement for additional analgesics. Various classes of adjuvants have been investigated in IVRA, including α2-adrenergic agonists such as dexmedetomidine, corticosteroids such as dexamethasone, opioids, ketamine, and nonsteroidal anti-inflammatory drugs **(31).**

Dexmedetomidine

Dexmedetomidine, a potent and highly selective α-2 adrenoceptor agonist, has been described as a unique sedative with analgesic, sympatholytic, and respiratory-preserving properties. It has been approved by the U.S. Food and Drug Administration for short-term sedation (< 24 h) of initially intubated and mechanically ventilated adult patients in the intensive care unit (ICU) and for sedation of non-intubated patients during surgical and other procedures. Although dexmedetomidine is now widely used for the above indications in the ICU and the operating room, its clinical applications have been greatly expanded in recent decades due to many favorable physiological effects **(31).**

Mechanism of action

The α2-AR agonists produce clinical effects after binding to G-Protein-coupled α2-AR, of which there are three subtypes (α2A, α2B, and α2C) with each having different physiological functions and pharmacological activities (Table 2). These receptor subtypes are found ubiquitously in the central, peripheral, and autonomic nervous systems, as well as in vital organs and blood vessels.

Dexmedetomidine is 8 to 10 times more selective towards α2-AR than clonidine. Neither clonidine nor dexmedetomidine is totally selective for any one of the α2-AR subtypes, but dexmedetomidine seems to have higher α2A-AR and α2C-AR affinity than clonidine. Locus ceruleus of the brain stem is the principal site for the sedative action and spinal cord is the principal site for the analgesic action, both acting through α2A-AR **(32).**

In the heart, the dominant action of α2-AR agonists is a decrease in tachycardia (through blocking cardioaccelerator nerve) and bradycardia via α2A-AR (through a vagomimetic action). In the peripheral vasculature, there is sympatholysis-mediated vasodilatation and smooth muscle cells receptor-mediated vasoconstriction. The mechanism for the antishivering and diuretic actions has yet to be established firmly. The responses to activation of the receptors in other areas include decreased salivation, decreased secretion, and decreased bowel motility in the gastrointestinal tract; contraction of vascular and other smooth muscle; inhibition of renin release, increased glomerular filtration, and increased secretion of sodium and water in the kidney; decreased intraocular pressure; and decreased insulin release from the pancreas. Combining all these effects, dexmedetomidine avoids some of the side effects of multiagent therapies **(33, 34).**

The analgesic and sedative effects of dexmedetomidine are primarily mediated through its action on alpha-2 adrenergic receptors, particularly at peripheral nerve endings, where it inhibits norepinephrine release. At the postsynaptic level, dexmedetomidine activates G-protein-coupled receptors, enhancing potassium conductance, which contributes to neuronal hyperpolarization and reduced nerve excitability. These mechanisms account for both its local analgesic effects and central sedation **(35).**

Table (2): Summary of alpha2 receptor subtypes and effects (36)

Location of the receptor	**Subtype of the receptor**	**Stimulation or inhibition**	**Effect**
Dorsal horn of the spinal cord	α2C and α2A	Stimulation	Reduced release of substance P and glutamate—leads to analgesia

Unmyelinated C-fibers	α2A and α2C	Hyperpolarization	Prolongation of sensory blockade
Prejunctional and postjunctional Vascular smooth muscle	α2A and α2B	Stimulation	Initial increase in arterial blood pressure, decreased heart rate, decreased blood pressure
Central nervous system locus coeruleus	α2C and α2A	Stimulation	Sedation, hypnosis

Pharmacokinetics

- **Absorption and distribution**

Dexmedetomidine exhibits linear pharmacokinetics in the recommended dose range of 0.2 to 0.7 μg/ kg/ hr administered as intravenous infusion up to 24 hours. The distribution phase is rapid, with a half-life of distribution of approximately 6 minutes and elimination half-life of 2 hours. The steady-state volume of distribution is 118 L. The average protein binding is 94% and is constant across the different plasma concentrations and also similar in males and females. It has negligible protein binding displacement by drugs commonly used during anesthesia and in the ICU like fentanyl, ketorolac, theophylline, digoxin, and lidocaine. Context-sensitive half-life ranges from 4 minutes after a 10-minute infusion to 250 minutes after an 8- hour infusion. Oral bioavailability is poor because of extensive first-pass metabolism. However, bioavailability of sublingually administered dexmedetomidine is high (84%), offering a potential role in pediatric sedation and premedication **(37).**

- **Metabolism and excretion**

Dexmedetomidine undergoes almost complete biotransformation through direct N-glucuronidation and cytochrome P-450 (CYP 2A6)-mediated aliphatic hydroxylation to inactive metabolites. Metabolites are excreted in the urine (about 95%) and in the feces (4%). Dose adjustments are required in patients with hepatic failure because of lower rate of metabolism **(38).**

Pharmacodynamics

- **Analgesic effects**

The analgesic properties of dexmedetomidine are mediated by several mechanisms, including spinal, supraspinal, and peripheral actions. However, the analgesic efficacy of dexmedetomidine is controversial. A ceiling effect has been shown in an ischemic pain model in healthy volunteers at doses > 0.5 μg/kg. However, in a cold pressor test, a dose-dependent analgesic effect was noted over a wide range of plasma concentrations from 0.5–8.0 ng/ml. The opioid-sparing effect of dexmedetomidine has been well documented in several clinical trials. Even as a sole analgesic, a 0.4 μg/kg dose of dexmedetomidine can be effectively used for pain relief after laparoscopic tubal ligation, although accompanying drowsiness and bradycardia may be undesirable side effects during the recovery period. Intraoperative dexmedetomidine administration for general anesthesia was superior to remifentanil administration, with lower pain scores during the first 24 postoperative hours and with less hypotension, shivering, and postoperative nausea and vomiting **(39, 40).**

Dexmedetomidine has anti-nociceptive effects on both somatic and visceral pain when administered via the neuraxial route. Neuraxial dexmedetomidine administration significantly decreases postoperative pain intensity and prolongs analgesic duration but with an increased risk of bradycardia. The potential application of dexmedetomidine

for the treatment and prevention of neuropathic pain has also been investigated. Local injection of dexmedetomidine was shown to produce an antiallodynic effect in spinal nerve ligation-induced neuropathic pain. Moreover, the use of pre-emptive intravenous dexmedetomidine reduces post-thoracotomy pain syndrome after coronary artery bypass surgery **(41, 42).**

- **Anesthetic adjuvant**

Dexmedetomidine can markedly reduce the anesthetic requirements of inhaled and intravenous anesthetics. It can also decrease the dose of opioids required, perioperatively and postoperatively, in patients undergoing a variety of surgical procedures. This opioid-sparing effect of dexmedetomidine decreases opioid use and thereby reduces the risk of opioid-induced respiratory depression in bariatric patients or those with significant respiratory disease **(43).**

- **In intravenous regional anesthesia**

Dexmedetomidine, a highly selective alpha-2 adrenergic agonist, has emerged as a valuable adjuvant in intravenous regional anesthesia (IVRA), particularly for upper limb surgeries. When combined with lignocaine, dexmedetomidine enhances the overall quality of anesthesia by producing faster onset of both sensory and motor blockade. It also significantly prolongs postoperative analgesia, improving patient comfort and reducing the need for additional pain medications after the procedure

(43).

A notable benefit of dexmedetomidine in IVRA is its ability to reduce tourniquet pain, a common and distressing complication of this technique. Patients receiving dexmedetomidine typically report lower pain scores and require less intraoperative opioid supplementation **(44).**

- **Adverse events**

Most of the adverse events associated with dexmedetomidine occur during or shortly after a loading infusion. A loading infusion often results in hypertension, hypotension, or bradycardia, which are closely related to the loading dose and infusion rate. The incidence of these adverse events can be prevented by slow bolus loading or by omitting bolus loading. In fact, many clinicians tend to avoid the administration of a loading dose, especially in critically ill patients. A slow titration to maintain the infusion rate of dexmedetomidine can also be helpful in preventing adverse events **(45).**

Although the incidence of severe bradycardia is low, there are some case reports of dexmedetomidine-related cardiac arrest. Cardiac conduction disorders, including left anterior fascicular block and first-degree AV block, and the co-administration of amiodarone and dexmedetomidine are potential factors contributing to the development of asystole, especially during general or regional anesthesia. In addition, caution should be taken when administering dexmedetomidine to patients with volume depletion or vasoconstriction. Adequate selection of patients and dosage is most important for the safe use of dexmedetomidine **(46).**

Dexamethasone

Dexamethasone has a wide variety of uses in the medical field. As a treatment, dexamethasone has been useful in treating acute exacerbations of multiple sclerosis, allergies, cerebral edema, inflammation, and shock. Patients with conditions such as asthma, atopic and contact dermatitis, and drug hypersensitivity reactions have benefited from dexamethasone. In endocrinology, dexamethasone has been found useful as a test for Cushing syndrome. Off-label indications are as follows. Dexamethasone is useful in the treatment of chemotherapy-induced nausea and vomiting. It is also used in the prevention and treatment of altitude sickness. It has also been used in the treatment of spinal cord compression due to metastases in oncological cases **(47).**

Mechanism of Action

Dexamethasone is a potent glucocorticoid with very little if any, mineralocorticoid activity. Dexamethasone's effect on the body occurs in a variety of ways. It works by suppressing the migration of neutrophils and decreasing lymphocyte colony proliferation. The capillary membrane becomes less permeable, as well. Lysosomal membranes have increased stability. There are higher concentrations of vitamin A compounds in the serum, prostaglandin, and some cytokines (interleukin-1, interleukin-12, interleukin-18, tumor necrosis factor, interferon-gamma, and granulocyte-macrophage colony-stimulating factor) become inhibited. Increased surfactant levels and improved pulmonary circulation have also been shown with dexamethasone. Dexamethasone is metabolized by the liver and excreted in the urine mainly **(48).**

Pharmacokinetics

According to the manufacturer's labeling, the pharmacokinetics of oral dexamethasone is dose-proportional between the dose range of 0.5 to 40 mg. Pharmacokinetic include: **(49)**

- Absorption: Dexamethasone median time to peak concentrations (Tmax) is 1 hour (range: 0.5 to 4 hours). A high-fat, high-calorie diet decreased C max by 23% of a single 20 mg dose of dexamethasone.
- Distribution: Dexamethasone is about 77% bound to human plasma proteins in vitro.
- Elimination: It has a biological half-life of approximately 36–54 hours, although its plasma elimination half-life is 3–5 hours, reflecting its prolonged genomic effects despite relatively rapid plasma clearance.
- Metabolism: it's metabolized in the liver, primarily by cytochrome P450 3A4 (CYP3A4), producing inactive metabolites.
- Excretion: Dexamethasone metabolites are eliminated mainly through the kidneys, while only a small fraction (<10%) of the administered dose is excreted unchanged in the urine.

Administration

Dexamethasone is available in various formulations for administration. It comes in tablet form, with strengths ranging from 0.5 mg to 6 mg. Other options include an injectable suspension and an oral solution. The specific formulations and strengths available are as follows: **(49)**

- Oral tablets: Dexamethasone tablets are available in strengths of 0.5 mg, 0.75 mg, 1 mg, 1.5 mg, 2 mg, 4 mg, 6 mg, and 20 mg.
- Oral elixir or solution: An oral solution is available in a concentration of 0.5 mg/5 mL.
- Oral concentrate: Dexamethasone Intensol is an oral concentrate with a concentration of 1 mg/mL. It is important to note that it contains alcohol.
- Injection (dexamethasone sodium phosphate): Dexamethasone is also available as an injectable suspension in different strengths, including 4 mg/mL, 20 mg/5 mL, 120 mg/30 mL, 10 mg/mL, and 100 mg/10 mL.

Adverse Effects

Dexamethasone, while generally well tolerated, is not without its drawbacks as a medication. Patients commonly report experiencing insomnia after its use, along with other frequent adverse effects such as acne, indigestion, fluid retention, electrolyte imbalances, weight gain, increased appetite, anorexia, nausea, vomiting, agitation, and depression. Additionally, there have been reports of more serious complications including adrenal suppression, arrhythmias, spermatogenic changes, glaucoma, hypokalemia, pulmonary edema, pseudotumor cerebri,

increased intracranial pressure, and the development of steroid-induced osteonecrosis of the femoral head with long-term treatment. Moreover, dexamethasone carries the risk of hepatotoxicity, which is well-established and can lead to liver injury when given in high doses, particularly through the reactivation of hepatitis-B or hepatocellular injury following high-dose treatment **(50).**

Contraindications

Dexamethasone use is contraindicated if patients have systemic fungal infections, hypersensitivity to dexamethasone, or cerebral malaria. Another contraindication is to administer live or live-attenuated vaccines during dexamethasone use. The immune system will be suppressed, placing the patient at risk of infection. It is still permissible to administer killed or inactivated vaccines. However, it bears mentioning that corticosteroids may attenuate immune response, and it is unpredictable if immunity develops. In patients with cirrhosis, diverticulitis, myasthenia gravis, renal insufficiency, or ulcerative diseases such as peptic ulcer disease or ulcerative colitis, it is important to use caution when prescribing dexamethasone. Recommendations include using dexamethasone cautiously during pregnancy as there is an increased risk of oral cleft formation **(51).**

Clinical experience has shown that large doses can increase blood pressure. In patients with recent myocardial infarction, it is advised to caution as an increase in free wall rupture of the left ventricle has been reported using dexamethasone. Suppression of the hypothalamus-pituitary-adrenal axis (HPA axis) occurs with use, and therefore the rapid withdrawal of dexamethasone is not recommended. It is important to gradually increase and decrease any corticosteroid due to its effect on the HPA axis. Latent diseases such as fungal (candida, cryptococcus, pneumocystis), parasitic (toxoplasmosis, amebiasis, Strongyloides), and bacterial (mycobacterium, Nocardia) infections may become active due to suppression of the immune system. Steroid use may inhibit bone formation and may lead to the formation of osteoporosis. Therefore, caution is necessary when prescribing dexamethasone to populations at higher risk for osteoporosis **(52).**

Monitoring during long-term use

Monitoring includes the following: **(49)**

- Serum electrolytes levels, blood pressure
- Serum glucose levels, HbA1c
- Periodic eye examination (long term dexamethasone increases the risk of cataracts and glaucoma)
- Bone mineral density scans
- Creatine kinase levels (long term use of glucocorticoids such as dexamethasone predisposes to myopathy; weakness is primarily proximal)

Toxicity

According to the manufacturer's labeling information, the oral LD50 of dexamethasone in female mice is 6.5 g/kg. The intravenous formulation of dexamethasone has an LD50 of 794 mg/kg in female mice. In the case of overdosage, no specific antidote is available. Therefore, treatment is supportive and symptomatic **(49).**

Ketamine

Ketamine is a dissociative anesthetic and NMDA receptor antagonist that has been investigated as an adjuvant in IVRA because of its analgesic and anti-hyperalgesic properties. Its analgesic effect is mainly mediated through blockade of NMDA receptors, in addition to interactions with opioid and monoaminergic pathways. However, its use may be associated with adverse effects such as dizziness, nausea, hallucinations, agitation, tachycardia, and hypertension, particularly after tourniquet deflation and systemic absorption. Therefore, caution is advised in patients

with cardiovascular disease, psychiatric disorders, or elevated intracranial pressure **(6, 53).**

Morphine

Morphine is a naturally occurring opioid analgesic. Its analgesic effects are mediated mainly through activation of peripheral and central μ-opioid receptors, leading to inhibition of nociceptive transmission. Peripheral opioid receptors become more active in inflamed tissues, which may explain the beneficial analgesic effect of morphine in IVRA. However, its use may be limited by opioid-related adverse effects including nausea, vomiting, pruritus, urinary retention, sedation, hypotension, and respiratory depression, especially after systemic absorption following tourniquet release. Morphine should therefore be used cautiously in elderly patients and those with respiratory or cardiovascular compromise **(54, 55).**

Fentanyl

Fentanyl is a potent synthetic opioid. It acts primarily through activation of μ-opioid receptors, resulting in inhibition of pain signal transmission. Some studies suggest that fentanyl may provide peripheral opioid-mediated analgesia before tourniquet release, although part of its analgesic effect may be related to systemic absorption after cuff deflation. Adverse effects include nausea, vomiting, pruritus, sedation, respiratory depression, bradycardia, and, rarely, chest wall rigidity at high doses. Careful use is recommended in patients with respiratory insufficiency, hepatic impairment, or opioid dependence **(56, 57).**

NSAIDs

Nonsteroidal anti-inflammatory drugs (NSAIDs), particularly ketorolac, tenoxicam, and lornoxicam, are among the most effective adjuvants used in IVRA. Their analgesic action is mainly mediated through inhibition of cyclooxygenase enzymes and suppression of prostaglandin synthesis, thereby reducing inflammatory pain transmission and peripheral sensitization. NSAIDs may also contribute to improved postoperative analgesia after tourniquet deflation. Nevertheless, their use may be associated with gastrointestinal irritation, nausea, renal impairment, platelet dysfunction, and bronchospasm in susceptible individuals. NSAIDs are contraindicated in patients with peptic ulcer disease, bleeding disorders, severe renal impairment, or hypersensitivity to aspirin or NSAIDs **(58).**

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