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A Review Study on "Levo-Bupivacaine"

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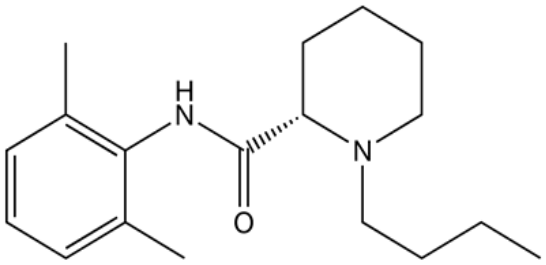
I. INTRODUCTION

- All Local anaesthetics (LA) agents have three characteristic portions :
  - A benzene ring - aromatic head
  - An intermediate chain
  - An amino group
- On the basis of intermediate portion of the molecule: Ester type and Amide type local anaesthetics.
- Ester group LA:-
  - Commonly cause allergic reactions
  - Have a short length of action.
  - Rapidly metabolized by cholinesterase.
- Amides:-
  - Rarely allergic reactions
  - But are more likely to cause toxic reactions if the dose is exceeded.

Chemical Structure:

- *Amide group LA having asymmetric carbon*
- *([2S]-1-butyl-N-[2, 6-dimethylphenyl] piperidine-2-carboxamide)*
- *Levo-enantiomer*



- $C_{18}H_{28}N_2O$

- **Chemical properties of three LA drugs**

	Bupivacaine	Ropivacaine	Levobupivacaine
Molecular weight	288	274	288
Liposolubility	30	2.8	30
Protein binding (%)	95	94	97

Pharmacokinetics

- Classic pharmacokinetic studies are usually performed using an intravenous application of the drug.
- Dose as well as route of administration - determines plasma concentration .
- Absorption dependent on vascularity of tissue.
- Volume of distribution estimated at 66.91 ± 18.23 L

- pKa 8.1,
- Half-life 3.3 hrs.
- Rate of clearance is 39.06 ± 13.29 L/hr .
- Depending on the pH, amino group can adopt tertiary or quaternary form.
- Protein binding –
- More than 97%, mainly to acid alpha1-glycoprotein, rather than to albumin.
- Racemic bupivacaine (95%) .
- Free levobupivacaine, even small fraction can have an action on other tissues, causing unwanted side-effects.
- In hypo-proteinaemic, undernourished pts, nephrotic pt & in newborn there is less protein for binding, causing higher levels of free drug, resulting in toxic effects - seen at lower doses.
- D isomer - lower threshold for causing tachycardia & dysrhythmias, than L isomer or racemic preparation which include,
- AV block,
- QRS widening
- Ventricular tachycardia &
- Fibrillation.

Experimental Studies

- Experimental animal study on rats suggested that...
- @ usual doses of 2mg/kg, all animals of dextro group developed apnoea, bradycardia, hypotension & finally died.
- No animal in levo group had apnoea & only 30% had a slight bradycardia.
- In sheep experiments racemic bupivacaine was administered in toxic quantities,
  - Conc. of dextro isomer was higher in myocardium & brain than conc.. of levo isomer.
  - Electrophysiological studies demonstrated that blockade of inactive sodium channels is stereoselective, with the D isomer being more potent & faster than the L-isomer. {higher cardiotoxicity A/with D isomer}.

Metabolism

- Extensively metabolised in the liver, primarily by cytochrome P450, especially CYP1A2 & CYP3A4 isoforms.
- Clearance is reduced when hepatic function is damaged.

When minimum concentration (MLAC) is reached to membranes of axons, molecules block sodium channels, in resting position & transmission of nerve impulses stops.
Onset time, duration of action & actions are quite similar to that of racemic substance.
Conc.. requird to produce cardiac & neurotoxicity; is higher for levobupivacaine than racemic bupivacaine.
"The safety margin is estimated at 1.3 which means that toxic effects are not seen until the concentration rises by 30%."

Clinical Applications

- **Subarachnoid block**
- Similar sensory & motor characteristics & recovery like bupivacaine.
- Minimum effective dose of levobupivacaine as recommended by an up- and-down sequential design study is 11.7 mg.
- **Epidural anaesthesia**
- Equal doses of levobupivacaine & bupivacaine (15 mL of 0.5%) provide similar onset of sensory block (8-30 min), maximum cephalic spread (T7-T8) & duration of analgesia (4-6 h).
- Continuous infusion of 15 mg/h of levobupivacaine provides effective pain relief in post-op period.
- **Wound infiltration**
- Post-incisional wound infiltration with 0.125% levobupivacaine provides more effective & longer duration of analgesia and early mobilization.
- Levobupivacaine has a positive effect on wound healing in earlier period, but had negative effects thereafter by↓sing wound tension strength.
- **Peripheral Nerve Blocks**
- Epinephrine does not prolong duration of sensory & motor block with levobupivacaine but may ↓se systemic toxicity.

- Addition of clonidine & fentanyl to levobupivacaine provide excellent analgesia & local anesthetic sparing effect & ↓se post-operative systemic morphine requirement.
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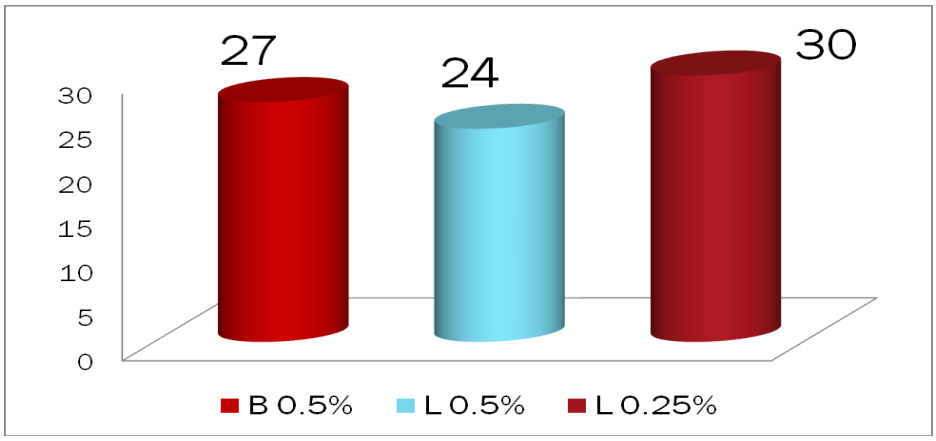
  ❖ "Onset Time, Quality of Blockade, and Duration of Three-in- One Blocks with Levobupivacaine and Bupivacaine" ***(Anesth Analg 2003;97:888 –92)***

  - No significant difference in sensory onset time among the three local anesthetic solutions was observed



❑ **Epidural labor analgesia**

- Levobupivacaine - provide adequate & safe labor analgesia, without significant influence on mode of delivery, duration of labor, or neonatal outcome.

❑ **Ophthalmic Surgery**

- 0.75% levobupivacaine provides more effective peribulbar anesthesia & more effective post-op analgesia for vitreo-retinal surgery compared with 0.75% ropivacaine.
- Topical anesthesia with levoisomer 0.75% - found to be more effective than lidocaine 2% in preventing pain & improving pt & surgeon comfort during cataract surgery, with less toxicity.

❑ **Pediatric Anesthesia**

➢ **Subarachnoid block**

◦ Dose for spinal anesthesia in neonates is slightly higher.

◦ Appropriate doses for infant spinal anesthesia are 1 mg/kg of isobaric 0.5% bupivacaine & ropivacaine and 1.2 mg/kg of isobaric 0.5% levobupivacaine

Caudal block : Recommended dose of levobupivacaine 2.5 mg/kg for lower abdominal surgery.

❑ Geriatric Anesthesia

- In view of safer pharmacological profile, levobupivacaine is considered to be a better local anesthetic than bupivacaine in geriatric population.

❑ **Adverse reactions**

- Hypotension (31%)
- Nausea (21%),
- Vomiting (14%),
- Headache (9%),
- Procedural pain (8%) &
- Dizziness (6%).

- **Contraindications:**

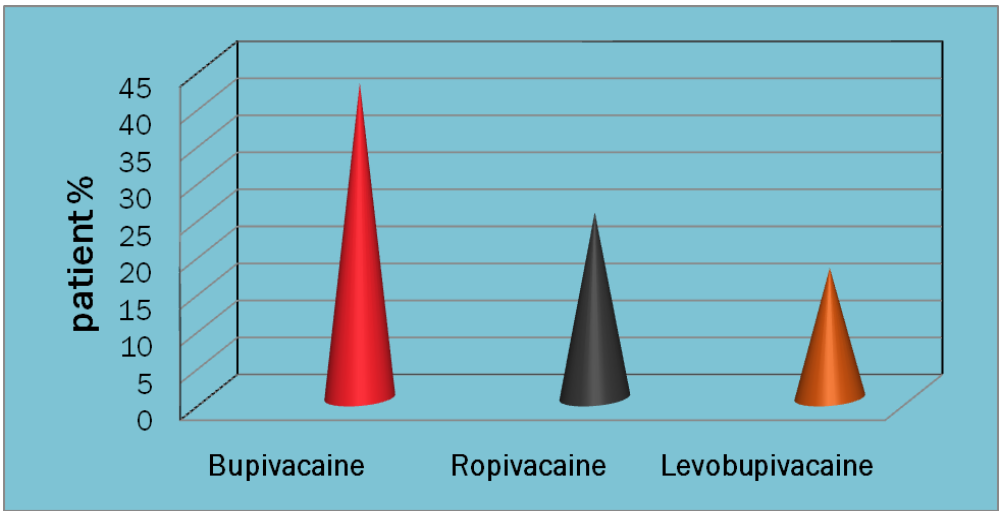
❑ Contraindicated for IVRA.

❑ Allergy for LA

❑ "Intraoperative hypotension requiring treatment with I.V. Ephedrin" ***(Acta Anaesth. Belg., 2008, 59, 65-71)***

Dosage Recommendations				
	Strength mg/mL	Dose (mL)	Dose (mg)	Motor Block
Surgical Anaesthesia				
Epidural For Surgery	5.0 - 7.5	10 - 20mL	50 -150mg	Moderate to Complete
Epidural For Caesarean Section	5.0	15 - 30mL	75 - 150mg	Moderate to Complete
Peripheral Nerve	2.5 - 5.0	1 - 40mL	Maximum 150mg	Moderate to Complete
Intrathecal	5.0	3mL	15mg	Moderate to Complete
Ophthalmic	7.5	5 - 15mL	37.5 - 112.5mg	Moderate to Complete
Local Infiltration - Adults	7.5	1 - 60mL	Maximum 150mg	Not applicable
Local Infiltration - Children < 12 yrs	2.5 - 5.0	0.25 - 0.50mL/kg	1.25 - 2.5mg/kg	Not applicable
Pain Management				
Labour Analgesia (epidural bolus)	2.5	10 - 20mL	25 - 50mg	Minimal to Moderate
Labour Analgesia (epidural infusion)	1.25[c]	4 - 10mL/h	5 - 12.5mg/h	Minimal to Moderate
Post-Operative Pain (epidural infusion)	1.25 - 2.5	10 - 15mL/h 5 - 7.5mL/h	12.5 - 18.75mg/h 12.5 - 18.75mg/h	Minimal to Moderate

❖ "Intraoperative hypotension requiring treatment with I.V. Ephedrin"
(Acta Anaesth. Belg., 2008, 59, 65-71)



- ***Toxicity & Management***
- Data suggest up to 20 out of 10,000 peripheral nerve blocks & 4 per 10,000 epidural blocks result in systemic local anaesthetic toxicity.
- Management -
  - Prevention by intermittent aspiration
  - Early Diagnosis
  - Aggressive fluid therapy
  - ACLS
  - Early 20% intralipid administration {0.5 ml/kg/min}
  - Cardiopulmonary bypass.