

RESEARCH MONOGRAPH . COMPOUND PROFILE

Bupivacaine

*A long-acting butyl-substituted
pipecoloxylidide racemic local anesthetic
with high cardiotoxicity that motivated
development of the (S)-enantiomer
levobupivacaine.*

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COMPOUND CLASS	Amide local anesthetic (long-acting)

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ABSTRACT

Bupivacaine (1-butyl-N-(2,6-dimethylphenyl)piperidine-2-carboxamide; CAS 2180-92-9; molecular formula C₁₈H₂₈N₂O; molecular weight 288.43) is a long-acting amide local anesthetic synthesized by Bo af Ekenstam at AB Bofors in 1957 and introduced clinically in 1965 (Marcaine, Sensorcaine). The compound is the n-butyl analog of mepivacaine and shares the piperidyl scaffold; the longer alkyl chain confers higher lipid solubility, longer duration, and greater protein binding. Bupivacaine is sold as a racemate of (R)- and (S)-enantiomers; the cardiotoxicity that distinguishes bupivacaine from shorter-acting amides is enantioselectively driven by the (R)-enantiomer, which has higher affinity for cardiac sodium channels and longer dissociation kinetics. Mechanism is voltage-gated sodium channel block, state-dependent and slowly dissociating, the slow kinetics underlying both the prolonged neural block and the elevated arrhythmogenic risk relative to lidocaine. Onset for infiltration is 5 to 10 minutes; duration is 4 to 8 hours, longer with epinephrine adjunct. Maximum recommended dose is 2.5 mg/kg without epinephrine and 3 mg/kg with epinephrine. The principal historical safety concern is cardiac arrest from inadvertent intravascular injection during regional anesthesia: bupivacaine binds the cardiac sodium channel and dissociates slowly, producing ventricular arrhythmias and refractory cardiovascular collapse that proved historically resistant to standard ACLS algorithms. Intravenous lipid emulsion (Intralipid 20 percent, 1.5 mL/kg bolus then 0.25 mL/kg/min infusion) is the rescue therapy, supported by case series and animal data showing reduction in cardiovascular collapse mortality. Bupivacaine remains widely

used for surgical regional anesthesia (spinal, epidural, peripheral nerve block) and obstetric epidural analgesia.

1. Compound Identification

Bupivacaine is described as amide local anesthetic (long-acting). A long-acting butyl-substituted pipecoloxylidide racemic local anesthetic with high cardiotoxicity that motivated development of the (S)-enantiomer levobupivacaine.

1.1 Class summary

Amide local anesthetic (long-acting)

1.2 Subtitle

A long-acting butyl-substituted pipecoloxylidide racemic local anesthetic with high cardiotoxicity that motivated development of the (S)-enantiomer levobupivacaine.

2. Abstract

Bupivacaine (1-butyl-N-(2,6-dimethylphenyl)piperidine-2-carboxamide; CAS 2180-92-9; molecular formula C₁₈H₂₈N₂O; molecular weight 288.43) is a long-acting amide local anesthetic synthesized by Bo af Ekenstam at AB Bofors in 1957 and introduced clinically in 1965 (Marcaine, Sensorcaine). The compound is the n-butyl analog of mepivacaine and shares the piperidylidide scaffold; the longer alkyl chain confers higher lipid solubility, longer duration, and greater protein binding. Bupivacaine is sold as a racemate of (R)- and (S)-enantiomers; the cardiotoxicity that distinguishes bupivacaine from shorter-acting amides is enantioselectively driven by the (R)-enantiomer, which has higher affinity for cardiac sodium channels and longer dissociation kinetics. Mechanism is voltage-gated sodium channel block, state-dependent and slowly dissociating, the slow kinetics underlying both the prolonged neural block and the elevated arrhythmogenic risk relative to lidocaine. Onset for infiltration is 5 to 10 minutes; duration is 4 to 8 hours, longer with epinephrine adjunct. Maximum recommended dose is 2.5 mg/kg without epinephrine and 3 mg/kg with epinephrine. The principal historical safety concern is cardiac arrest from inadvertent intravascular injection during regional anesthesia: bupivacaine binds the cardiac sodium channel and dissociates slowly, producing ventricular arrhythmias and refractory cardiovascular collapse that proved historically resistant to standard ACLS algorithms. Intravenous lipid emulsion (Intralipid 20 percent, 1.5 mL/kg bolus then 0.25 mL/kg/min infusion) is the rescue therapy, supported by case series and animal data showing reduction in cardiovascular collapse mortality. Bupivacaine remains widely used for surgical regional anesthesia (spinal, epidural, peripheral nerve block) and obstetric epidural analgesia.

3. Mechanism of Action

Slowly-dissociating voltage-gated sodium channel block. Cardiotoxicity primarily driven by (R)-enantiomer affinity for cardiac sodium channels.

The mechanistic profile described above represents the consensus position from peer-reviewed literature where available; for compounds with sparse formal characterization, this section reflects vendor-grade reports and structurally-related class pharmacology and should be interpreted with appropriate caution.

4. Pharmacokinetics and Routes of Administration

Pharmacokinetic data are summarized within the abstract for compounds with formal Phase 1 records. Compounds without published human pharmacokinetic studies are noted as such; investigators should treat the absence of data as a research limitation.

5. Reported Research Dose Ranges

2.5 mg/kg without epinephrine, 3 mg/kg with epinephrine. Spinal 5 to 15 mg, epidural 50 to 150 mg.

Doses are scaled from clinical use where the compound is approved as a medicine, from Phase 2/3 trials where development advanced, or from rodent dose-response data scaled by allometric assumptions where the compound has no human clinical record. Investigators should treat dose ranges from research-chemical-grade vendors as starting points for their own pharmacokinetic and tolerability characterization rather than validated dosing recommendations.

6. Sourcing and Quality Verification

Investigators should obtain analytical confirmation of identity (mass spectrometry; for peptides, additionally amino acid analysis or N-terminal sequencing) and purity (HPLC area-percent, ideally greater than 95 percent) on every lot. Vendor certificates of analysis vary in quality; third-party analytical confirmation through independent laboratories (e.g., Janoshik Analytical, Anabolic Lab) is the gold standard for research-grade peptides and small molecules.

For compounds with established pharmaceutical-grade marketing in any jurisdiction, sourcing from the marketed product (where legal and accessible) provides the highest quality assurance.

7. Reconstitution and Handling

Peptides should be reconstituted in bacteriostatic water or sterile water for injection in the volume appropriate to the desired concentration; lyophilized peptides should be allowed to come to room temperature before reconstitution to minimize precipitation. Reconstituted peptides should be stored refrigerated and used within the timeframe specified by the manufacturer (typically 14 to 30 days for bacteriostatic water reconstitutions, shorter for sterile water).

Small molecules: storage conditions vary by compound; consult the certificate of analysis for the specific product. Most are stable at room temperature in dry, dark conditions; oxidation-sensitive compounds (e.g., catecholamine precursors) require cool storage and protection from light.

8. Stack Interaction Considerations

Investigators combining this compound with other research substances should consider receptor-level interactions (additive effects at shared targets), enzyme-level interactions (CYP-mediated drug-drug interactions where applicable), and pharmacodynamic interactions (additive sedation, additive serotonergic activity, additive hemodynamic effects).

The stack interaction section in published monographs of well-characterized compounds is necessarily incomplete for any specific combination; investigators should treat novel combinations with elevated caution and titrate gradually.

9. References

1. Albright GA. Cardiac arrest following regional anesthesia with etidocaine or bupivacaine. Anesthesiology 1979.
2. Clarkson CW, Hondeghem LM. Mechanism for bupivacaine depression of cardiac conduction. Anesthesiology 1985.
3. Weinberg GL, et al. Pretreatment or resuscitation with a lipid infusion shifts the dose-response to bupivacaine-induced asystole. Anesthesiology 1998.

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