

RESEARCH MONOGRAPH . COMPOUND PROFILE

Lidocaine

The prototype amide local anesthetic introduced in 1948, with concurrent indications as an intravenous antiarrhythmic and analgesic adjunct.

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ABSTRACT

Lidocaine (2-(diethylamino)-N-(2,6-dimethylphenyl)acetamide; CAS 137-58-6; molecular formula C₁₄H₂₂N₂O; molecular weight 234.34) is the prototype amide-class local anesthetic, synthesized by Nils Lofgren and Bengt Lundqvist at AB Astra in 1943 and introduced clinically in 1948 (Xylocaine). The compound replaced procaine and the ester-class anesthetics as the first-line choice owing to faster onset, longer duration, and substantially lower allergic potential (the amide linkage is metabolized hepatically rather than producing the para-aminobenzoic acid metabolite of ester anesthetics, the dominant allergen in that class). Mechanism is voltage-gated sodium channel blockade, predominantly at the inactivated state, with state-dependent kinetics that produce greater block in rapidly firing tissues (the basis for both local anesthetic action on small unmyelinated C fibers and antiarrhythmic action on ventricular tissue). The pK_a is 7.9; at physiologic pH approximately 25 percent of the molecule is uncharged and able to cross neural and cardiac membranes, with reprotonation in the cytoplasm to engage the sodium channel pore from the intracellular side. Onset is fast (1 to 5 minutes for infiltration); duration is 1 to 2 hours unless coadministered with epinephrine, which extends duration to 3 to 4 hours through vasoconstriction and reduced systemic absorption. Maximum recommended dose for infiltration is 4.5 mg/kg without epinephrine and 7 mg/kg with epinephrine. Systemic toxicity (LAST, local anesthetic systemic toxicity) presents at plasma concentrations above 5 micrograms/mL with progression from perioral numbness, tinnitus, and metallic taste through generalized seizures to cardiovascular collapse; intravenous lipid

emulsion (Intralipid 20 percent) is the rescue therapy. Antiarrhythmic indications are ventricular arrhythmias particularly in the postinfarction period; lidocaine is largely displaced by amiodarone in advanced cardiac life support but retains a role in specific contexts.

1. Compound Identification

Lidocaine is described as amide local anesthetic and class Ib antiarrhythmic. The prototype amide local anesthetic introduced in 1948, with concurrent indications as an intravenous antiarrhythmic and analgesic adjunct.

1.1 Class summary

Amide local anesthetic and class IB antiarrhythmic

1.2 Subtitle

The prototype amide local anesthetic introduced in 1948, with concurrent indications as an intravenous antiarrhythmic and analgesic adjunct.

2. Abstract

Lidocaine (2-(diethylamino)-N-(2,6-dimethylphenyl)acetamide; CAS 137-58-6; molecular formula C₁₄H₂₂N₂O; molecular weight 234.34) is the prototype amide-class local anesthetic, synthesized by Nils Lofgren and Bengt Lundqvist at AB Astra in 1943 and introduced clinically in 1948 (Xylocaine). The compound replaced procaine and the ester-class anesthetics as the first-line choice owing to faster onset, longer duration, and substantially lower allergic potential (the amide linkage is metabolized hepatically rather than producing the para-aminobenzoic acid metabolite of ester anesthetics, the dominant allergen in that class). Mechanism is voltage-gated sodium channel blockade, predominantly at the inactivated state, with state-dependent kinetics that produce greater block in rapidly firing tissues (the basis for both local anesthetic action on small unmyelinated C fibers and antiarrhythmic action on ventricular tissue). The pK_a is 7.9; at physiologic pH approximately 25 percent of the molecule is uncharged and able to cross neural and cardiac membranes, with reprotonation in the cytoplasm to engage the sodium channel pore from the intracellular side. Onset is fast (1 to 5 minutes for infiltration); duration is 1 to 2 hours unless coadministered with epinephrine, which extends duration to 3 to 4 hours through vasoconstriction and reduced systemic absorption. Maximum recommended dose for infiltration is 4.5 mg/kg without epinephrine and 7 mg/kg with epinephrine. Systemic toxicity (LAST, local anesthetic systemic toxicity) presents at plasma concentrations above 5 micrograms/mL with progression from perioral numbness, tinnitus, and metallic taste through generalized seizures to cardiovascular collapse; intravenous lipid emulsion (Intralipid 20 percent) is the rescue therapy. Antiarrhythmic indications are ventricular arrhythmias particularly in the postinfarction period; lidocaine is largely displaced by amiodarone in advanced cardiac life support but retains a role in specific contexts.

3. Mechanism of Action

Voltage-gated sodium channel blockade, state-dependent (preferential block of inactivated channel state). Tonic and use-dependent components.

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

Infiltration 4.5 mg/kg without epinephrine, 7 mg/kg with epinephrine. IV antiarrhythmic 1 to 1.5 mg/kg bolus then 1 to 4 mg/min infusion.

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. Catterall WA, Mackie K. Local anesthetics. Goodman and Gilman 14e.
2. Neal JM, et al. ASRA Practice Advisory on Local Anesthetic Systemic Toxicity. Reg Anesth Pain Med 2018.
3. Hille B. Local anesthetics: hydrophilic and hydrophobic pathways for the drug-receptor reaction. J Gen Physiol 1977.
4. Weinberg GL. Lipid emulsion infusion: resuscitation for local anesthetic and other drug overdose. Anesthesiology 2012.

This monograph is provided for research use only. Not for medical, diagnostic, or therapeutic purposes. Not for human consumption. Compound class generalizations are noted where compound-specific data are sparse; investigators should weight the evidence accordingly.