

RESEARCH MONOGRAPH . COMPOUND PROFILE

Chloroprocaine

A 2-chloro-substituted procaine analog with the fastest plasma cholinesterase hydrolysis among local anesthetics, used in obstetric epidural and short-procedure spinal anesthesia.

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ABSTRACT

Chloroprocaine (2-(diethylamino)ethyl 4-amino-2-chlorobenzoate; CAS 133-16-4; molecular formula C₁₃H₁₉ClN₂O₂; molecular weight 270.76) is an ester-class local anesthetic introduced in the 1950s (Nesacaine) as a 2-chloro analog of procaine. The 2-chloro substitution adjacent to the ester linkage substantially accelerates plasma cholinesterase hydrolysis, producing the shortest plasma half-life of any clinical local anesthetic (approximately 21 seconds, versus 1 minute for procaine and far longer for amides). The very short systemic exposure makes chloroprocaine the safest local anesthetic for fetal exposure during obstetric epidural anesthesia and a useful agent for short-procedure spinal anesthesia in ambulatory surgical centers where rapid offset and discharge readiness are operationally valuable. Mechanism is voltage-gated sodium channel block with state-dependent kinetics; potency is similar to procaine on a milligram basis and substantially less than amide agents. The historical association with neurotoxicity (cauda equina syndrome) traces to the bisulfite preservative formulation used in Nesacaine through the 1980s and a high-pH, sodium bisulfite preservative system that produced free radical injury to nerve roots when administered intrathecally; reformulation with EDTA preservative and subsequent preservative-free 1 percent and 3 percent preparations resolved the neurotoxicity concern, and chloroprocaine has returned to spinal anesthesia use in ambulatory surgery as an alternative to lidocaine spinal (which carries its own transient neurologic symptoms concern). Modern formulations are preservative-free or use methylparaben preservatives at concentrations below the historical threshold for

nerve injury. Maximum recommended doses are 11 mg/kg without epinephrine and 14 mg/kg with epinephrine.

1. Compound Identification

Chloroprocaine is described as ester local anesthetic (very short-acting). A 2-chloro-substituted procaine analog with the fastest plasma cholinesterase hydrolysis among local anesthetics, used in obstetric epidural and short-procedure spinal anesthesia.

1.1 Class summary

Ester local anesthetic (very short-acting)

1.2 Subtitle

A 2-chloro-substituted procaine analog with the fastest plasma cholinesterase hydrolysis among local anesthetics, used in obstetric epidural and short-procedure spinal anesthesia.

2. Abstract

Chloroprocaine (2-(diethylamino)ethyl 4-amino-2-chlorobenzoate; CAS 133-16-4; molecular formula C₁₃H₁₉ClN₂O₂; molecular weight 270.76) is an ester-class local anesthetic introduced in the 1950s (Nesacaine) as a 2-chloro analog of procaine. The 2-chloro substitution adjacent to the ester linkage substantially accelerates plasma cholinesterase hydrolysis, producing the shortest plasma half-life of any clinical local anesthetic (approximately 21 seconds, versus 1 minute for procaine and far longer for amides). The very short systemic exposure makes chloroprocaine the safest local anesthetic for fetal exposure during obstetric epidural anesthesia and a useful agent for short-procedure spinal anesthesia in ambulatory surgical centers where rapid offset and discharge readiness are operationally valuable. Mechanism is voltage-gated sodium channel block with state-dependent kinetics; potency is similar to procaine on a milligram basis and substantially less than amide agents. The historical association with neurotoxicity (cauda equina syndrome) traces to the bisulfite preservative formulation used in Nesacaine through the 1980s and a high-pH, sodium bisulfite preservative system that produced free radical injury to nerve roots when administered intrathecally; reformulation with EDTA preservative and subsequent preservative-free 1 percent and 3 percent preparations resolved the neurotoxicity concern, and chloroprocaine has returned to spinal anesthesia use in ambulatory surgery as an alternative to lidocaine spinal (which carries its own transient neurologic symptoms concern). Modern formulations are preservative-free or use methylparaben preservatives at concentrations below the historical threshold for nerve injury. Maximum recommended doses are 11 mg/kg without epinephrine and 14 mg/kg with epinephrine.

3. Mechanism of Action

Voltage-gated sodium channel block. Very rapid plasma cholinesterase hydrolysis (half-life ~21 seconds).

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

11 mg/kg without epinephrine, 14 mg/kg with epinephrine. Spinal 30 to 60 mg, epidural 300 to 600 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. Smith KN, et al. Spinal 2-chloroprocaine: a comparison with small-dose bupivacaine. *Anesthesiology* 2004.
2. Reisner LS, et al. Persistent neurologic deficit after intrathecal 2-chloroprocaine. *Anesth Analg* 1980.
3. Goldblum E, Atchabahian A. The use of 2-chloroprocaine for spinal anaesthesia. *Acta Anaesthesiol Scand* 2013.

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