

RESEARCH MONOGRAPH . COMPOUND PROFILE

Methohexital

An ultrashort-acting methylated oxybarbiturate with faster recovery than thiopental, used principally for electroconvulsive therapy and brief procedural anesthesia.

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COMPOUND CLASS	Methylated oxybarbiturate intravenous anesthetic

ABSTRACT

Methohexital sodium (alpha-DL-1-methyl-5-allyl-5-(1-methyl-2-pentynyl)barbituric acid sodium; CAS 22151-68-4; molecular formula $C_{14}H_{17}N_2NaO_3$; molecular weight 284.29 free acid) is a methylated oxybarbiturate intravenous anesthetic synthesized by Eli Lilly in 1956 and introduced clinically as Brevital in 1960. The compound differs from thiopental in retaining oxygen at the 2-position (oxybarbiturate rather than thiobarbiturate) and carrying a methyl group on the N-1 nitrogen. The 1-methyl substitution accelerates hepatic metabolism (clearance approximately 4-fold faster than thiopental on a milligram basis) and shortens elimination half-life to approximately 4 hours, enabling faster awakening with minimal residual sedation after a single induction dose. Mechanism is GABA-A positive allosteric modulation at the barbiturate site, identical to thiopental. The principal clinical niches in modern practice are electroconvulsive therapy (where the brief duration enables rapid recovery in serial-ECT outpatient settings) and brief procedural sedation in patients with contraindications to propofol. Methohexital is the dominant induction agent for ECT in many practices owing to its minimal anticonvulsant effect at induction doses (versus propofol and thiopental, which raise seizure threshold and shorten ECT seizure duration, requiring higher electrical stimulus). Cardiovascular and respiratory effects are similar to thiopental. The principal historical safety concerns are myoclonus on injection (a propofol-class adverse event also seen with methohexital) and the standard barbiturate contraindications (porphyria; the 1-methyl substitution does not eliminate the porphyrinogenic effect). Maximum recommended dose for induction is 1 to 1.5 mg/kg.

1. Compound Identification

Methohexital is described as methylated oxybarbiturate intravenous anesthetic. An ultrashort-acting methylated oxybarbiturate with faster recovery than thiopental, used principally for electroconvulsive therapy and brief procedural anesthesia.

1.1 Class summary

Methylated oxybarbiturate intravenous anesthetic

1.2 Subtitle

An ultrashort-acting methylated oxybarbiturate with faster recovery than thiopental, used principally for electroconvulsive therapy and brief procedural anesthesia.

2. Abstract

Methohexital sodium (alpha-DL-1-methyl-5-allyl-5-(1-methyl-2-pentynyl)barbituric acid sodium; CAS 22151-68-4; molecular formula $C_{14}H_{17}N_2NaO_3$; molecular weight 284.29 free acid) is a methylated oxybarbiturate intravenous anesthetic synthesized by Eli Lilly in 1956 and introduced clinically as Brevital in 1960. The compound differs from thiopental in retaining oxygen at the 2-position (oxybarbiturate rather than thiobarbiturate) and carrying a methyl group on the N-1 nitrogen. The 1-methyl substitution accelerates hepatic metabolism (clearance approximately 4-fold faster than thiopental on a milligram basis) and shortens elimination half-life to approximately 4 hours, enabling faster awakening with minimal residual sedation after a single induction dose. Mechanism is GABA-A positive allosteric modulation at the barbiturate site, identical to thiopental. The principal clinical niches in modern practice are electroconvulsive therapy (where the brief duration enables rapid recovery in serial-ECT outpatient settings) and brief procedural sedation in patients with contraindications to propofol. Methohexital is the dominant induction agent for ECT in many practices owing to its minimal anticonvulsant effect at induction doses (versus propofol and thiopental, which raise seizure threshold and shorten ECT seizure duration, requiring higher electrical stimulus). Cardiovascular and respiratory effects are similar to thiopental. The principal historical safety concerns are myoclonus on injection (a propofol-class adverse event also seen with methohexital) and the standard barbiturate contraindications (porphyria; the 1-methyl substitution does not eliminate the porphyrinogenic effect). Maximum recommended dose for induction is 1 to 1.5 mg/kg.

3. Mechanism of Action

GABA-A positive allosteric modulation at the barbiturate site. Faster hepatic metabolism than thiopental drives the shorter clinical duration.

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

Induction 1 to 1.5 mg/kg IV. ECT induction 0.5 to 1 mg/kg.

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. Reves JG, et al. Pharmacology of intravenous anesthetic induction drugs. Anesthesiology 2007.
2. Folk JW, et al. Anesthesia for electroconvulsive therapy. J Anesth 2000.

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.