

RESEARCH MONOGRAPH . COMPOUND PROFILE

Thiopental

The first ultrashort-acting barbiturate intravenous anesthetic, dominant for induction from 1934 through the 1990s, displaced by propofol but retained for cerebral protection.

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ABSTRACT

Thiopental sodium (sodium 5-ethyl-5-(pentan-2-yl)-2-thioxopyrimidine-4,6(1H,5H)-dione; CAS 76-75-5; molecular formula $C_{11}H_{17}N_2NaO_2S$; molecular weight 264.32 free acid) is a thiobarbiturate intravenous anesthetic synthesized by Ernest Volwiler and Donalee Tabern at Abbott Laboratories in 1932 and introduced clinically by John Lundy at the Mayo Clinic in 1934 (Pentothal). The compound is the canonical ultrashort-acting barbiturate; substitution of sulfur for oxygen at the 2-position substantially increases lipid solubility relative to oxybarbiturates, enabling rapid blood-brain crossing and a sleep onset within one circulation time (approximately 30 seconds). Mechanism is positive allosteric modulation of GABA-A receptors at the barbiturate site, distinct from the benzodiazepine site, with prolongation of GABA chloride channel open time. At higher concentrations barbiturates can directly open GABA-A channels in the absence of GABA. Pharmacokinetics: thiopental redistribution from brain to muscle and fat is responsible for the brief clinical effect (approximately 10 minutes from a single induction dose), not metabolic clearance; hepatic metabolism is slow (half-life 8 to 12 hours) and accumulating doses produce prolonged emergence. Cardiovascular effects include dose-dependent myocardial depression and reduction in systemic vascular resistance with reflex tachycardia. Respiratory effects include apnea at induction doses. The cerebral effects (reduction in cerebral metabolic rate and cerebral blood flow with relatively preserved cerebral perfusion pressure) underlie the use of thiopental in raised intracranial pressure and the so-called barbiturate coma in refractory status epilepticus. Propofol

displaced thiopental as the dominant induction agent in the 1990s. Thiopental was the historical first agent in the three-drug US lethal injection protocol; manufacturing supply was withdrawn from US execution use after 2010.

1. 1. Compound Identification

Thiopental is described as thiobarbiturate intravenous anesthetic. The first ultra-short-acting barbiturate intravenous anesthetic, dominant for induction from 1934 through the 1990s, displaced by propofol but retained for cerebral protection.

1.1. 1.1 Class summary

Thiobarbiturate intravenous anesthetic

1.2. 1.2 Subtitle

The first ultrashort-acting barbiturate intravenous anesthetic, dominant for induction from 1934 through the 1990s, displaced by propofol but retained for cerebral protection.

2. Abstract

Thiopental sodium (sodium 5-ethyl-5-(pentan-2-yl)-2-thioxopyrimidine-4,6(1H,5H)-dione; CAS 76-75-5; molecular formula C₁₁H₁₇N₂NaO₂S; molecular weight 264.32 free acid) is a thiobarbiturate intravenous anesthetic synthesized by Ernest Volwiler and Donalee Tabern at Abbott Laboratories in 1932 and introduced clinically by John Lundy at the Mayo Clinic in 1934 (Pentothal). The compound is the canonical ultrashort-acting barbiturate; substitution of sulfur for oxygen at the 2-position substantially increases lipid solubility relative to oxybarbiturates, enabling rapid blood-brain crossing and a sleep onset within one circulation time (approximately 30 seconds). Mechanism is positive allosteric modulation of GABA-A receptors at the barbiturate site, distinct from the benzodiazepine site, with prolongation of GABA chloride channel open time. At higher concentrations barbiturates can directly open GABA-A channels in the absence of GABA. Pharmacokinetics: thiopental redistribution from brain to muscle and fat is responsible for the brief clinical effect (approximately 10 minutes from a single induction dose), not metabolic clearance; hepatic metabolism is slow (half-life 8 to 12 hours) and accumulating doses produce prolonged emergence. Cardiovascular effects include dose-dependent myocardial depression and reduction in systemic vascular resistance with reflex tachycardia. Respiratory effects include apnea at induction doses. The cerebral effects (reduction in cerebral metabolic rate and cerebral blood flow with relatively preserved cerebral perfusion pressure) underlie the use of thiopental in raised intracranial pressure and the so-called barbiturate coma in refractory status epilepticus. Propofol displaced thiopental as the dominant induction agent in the 1990s. Thiopental was the historical first agent in the three-drug US lethal injection protocol; manufacturing supply was withdrawn from US execution use after 2010.

3. Mechanism of Action

GABA-A positive allosteric modulation at the barbiturate site, prolonging chloride channel open time. Direct channel opening at higher concentrations.

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. 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. 5. Reported Research Dose Ranges

Induction 3 to 5 mg/kg IV. Cerebral protection 10 to 30 mg/kg in divided doses. Status epilepticus 5 to 15 mg/kg load.

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. 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. 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. 9. References

1. Lundy JS. Intravenous anesthesia with thiobarbiturates. Proc Mayo Clinic 1935.
2. Olsen RW. Molecular mechanism of action of general anesthetics. Toxicol Lett 1998.
3. Reves JG, et al. Pharmacology of intravenous anesthetic induction drugs. Anesthesiology 2007.

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