

RESEARCH MONOGRAPH . COMPOUND PROFILE

Isoflurane

A halogenated methyl ethyl ether introduced in 1981 that remained the dominant inhalational anesthetic of the 1990s before sevoflurane and desflurane displaced it.

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AUTHOR	Kodiac biolabs Research
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ABSTRACT

Isoflurane (1-chloro-2,2,2-trifluoroethyl difluoromethyl ether; CAS 26675-46-7; molecular formula $C_3H_2ClF_5O$; molecular weight 184.49) is a halogenated methyl ethyl ether volatile anesthetic introduced clinically by Ohio Medical Products in 1981. The minimum alveolar concentration (MAC) at 40 years of age is 1.15 percent in oxygen and 0.5 percent in 70 percent nitrous oxide. The blood-gas partition coefficient is 1.4, intermediate between halothane (2.4) and the modern agents desflurane (0.42) and sevoflurane (0.65); this corresponds to moderately fast induction and emergence relative to halothane but substantially slower than desflurane. Mechanism is multifactorial and incompletely characterized: principal targets include positive allosteric modulation of GABA-A receptors at sites distinct from benzodiazepine and barbiturate sites, two-pore domain potassium channel (TREK-1, TASK) activation, glycine receptor potentiation, and inhibition of NMDA glutamate currents at clinically relevant partial pressures. Cardiovascular effects include dose-dependent reduction in systemic vascular resistance and modest negative inotropy with preserved cardiac output through reflex tachycardia; coronary vasodilation has been studied for steal physiology but the clinical significance is limited. Respiratory effects include dose-dependent depression of tidal volume with compensatory tachypnea. Hepatotoxicity through trifluoroacetylated protein adduct formation occurs in 0.2 percent of metabolism (versus 20 percent for halothane) and the clinical incidence of immune-mediated hepatitis is correspondingly low. Used widely in veterinary anesthesia and in lower-resource

settings where acquisition cost favors isoflurane over the newer agents.

1. Compound Identification

Isoflurane is described as halogenated ether volatile general anesthetic. A halogenated methyl ethyl ether introduced in 1981 that remained the dominant inhalational anesthetic of the 1990s before sevoflurane and desflurane displaced it.

1.1 Class summary

Halogenated ether volatile general anesthetic

1.2 Subtitle

A halogenated methyl ethyl ether introduced in 1981 that remained the dominant inhalational anesthetic of the 1990s before sevoflurane and desflurane displaced it.

2. Abstract

Isoflurane (1-chloro-2,2,2-trifluoroethyl difluoromethyl ether; CAS 26675-46-7; molecular formula $C_3H_2ClF_5O$; molecular weight 184.49) is a halogenated methyl ethyl ether volatile anesthetic introduced clinically by Ohio Medical Products in 1981. The minimum alveolar concentration (MAC) at 40 years of age is 1.15 percent in oxygen and 0.5 percent in 70 percent nitrous oxide. The blood-gas partition coefficient is 1.4, intermediate between halothane (2.4) and the modern agents desflurane (0.42) and sevoflurane (0.65); this corresponds to moderately fast induction and emergence relative to halothane but substantially slower than desflurane. Mechanism is multifactorial and incompletely characterized: principal targets include positive allosteric modulation of GABA-A receptors at sites distinct from benzodiazepine and barbiturate sites, two-pore domain potassium channel (TREK-1, TASK) activation, glycine receptor potentiation, and inhibition of NMDA glutamate currents at clinically relevant partial pressures. Cardiovascular effects include dose-dependent reduction in systemic vascular resistance and modest negative inotropy with preserved cardiac output through reflex tachycardia; coronary vasodilation has been studied for steal physiology but the clinical significance is limited. Respiratory effects include dose-dependent depression of tidal volume with compensatory tachypnea. Hepatotoxicity through trifluoroacetylated protein adduct formation occurs in 0.2 percent of metabolism (versus 20 percent for halothane) and the clinical incidence of immune-mediated hepatitis is correspondingly low. Used widely in veterinary anesthesia and in lower-resource settings where acquisition cost favors isoflurane over the newer agents.

3. Mechanism of Action

Multifactorial: GABA-A positive modulation, K2P channel activation (TREK-1, TASK), glycine receptor potentiation, NMDA inhibition. Composite effect produces unconsciousness, amnesia, and immobility.

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

MAC 1.15 percent in oxygen at age 40; clinical maintenance 0.8 to 1.5 percent end-tidal.

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. Eger EI 2nd. Isoflurane: a review. Anesthesiology 1981.
2. Franks NP, Lieb WR. Molecular and cellular mechanisms of general anaesthesia. Nature 1994.
3. Hemmings HC Jr, et al. Emerging molecular mechanisms of general anesthetic action. Trends Pharmacol Sci 2005.
4. Jones RM. Desflurane and sevoflurane: inhalation anaesthetics for this decade? Br J Anaesth 1990.

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