

RESEARCH MONOGRAPH . COMPOUND PROFILE

Enflurane

The immediate predecessor to isoflurane in the Terrell ether series, marketed as Ethrane, displaced by isoflurane owing to electroencephalographic seizure activity at high concentrations.

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ABSTRACT

Enflurane (2-chloro-1,1,2-trifluoroethyl difluoromethyl ether; CAS 13838-16-9; molecular formula $C_3H_2ClF_5O$; molecular weight 184.49) is a halogenated methyl ethyl ether developed by Ross Terrell at Ohio Medical Products in the structure-activity series that produced both enflurane (1963) and its structural isomer isoflurane (1965). Enflurane reached clinical use in 1972 (Ethrane) and was widely used through the 1980s before isoflurane displaced it. The minimum alveolar concentration (MAC) at age 40 is 1.68 percent in oxygen; the blood-gas partition coefficient is 1.9, intermediate between halothane and isoflurane. Mechanism parallels other volatile anesthetics (GABA-A, K2P, glycine, NMDA modulation). The principal clinical limitation is dose-dependent generation of high-amplitude epileptiform activity on electroencephalography, particularly at end-tidal concentrations above 2.5 percent and during hypocapnia, with occasional clinical seizures during deep anesthesia. The mechanism of enflurane epileptogenesis is incompletely characterized but appears to involve thalamocortical disinhibition at concentrations where cortical inhibition exceeds cortical excitatory tone. This electrophysiological profile contraindicates enflurane in patients with seizure disorders and contributed substantially to its displacement by isoflurane, the structural isomer with similar clinical profile but absent the epileptiform signal. Hepatic metabolism is approximately 2 to 5 percent (intermediate between halothane and isoflurane); fluoride generation is sufficient to raise plasma concentrations into the historically nephrotoxic range during very prolonged exposures. Cardiovascular effects include modest myocardial depression and dose-dependent vasodilation.

Clinical use of enflurane has nearly disappeared in developed economies; it remains available as a research tool for halogenated ether structure-activity studies.

1. Compound Identification

Enflurane is described as halogenated ether volatile general anesthetic. The immediate predecessor to isoflurane in the Terrell ether series, marketed as Ethrane, displaced by isoflurane owing to electroencephalographic seizure activity at high concentrations.

1.1 Class summary

Halogenated ether volatile general anesthetic

1.2 Subtitle

The immediate predecessor to isoflurane in the Terrell ether series, marketed as Ethrane, displaced by isoflurane owing to electroencephalographic seizure activity at high concentrations.

2. Abstract

Enflurane (2-chloro-1,1,2-trifluoroethyl difluoromethyl ether; CAS 13838-16-9; molecular formula $C_3H_2ClF_5O$; molecular weight 184.49) is a halogenated methyl ethyl ether developed by Ross Terrell at Ohio Medical Products in the structure-activity series that produced both enflurane (1963) and its structural isomer isoflurane (1965). Enflurane reached clinical use in 1972 (Ethrane) and was widely used through the 1980s before isoflurane displaced it. The minimum alveolar concentration (MAC) at age 40 is 1.68 percent in oxygen; the blood-gas partition coefficient is 1.9, intermediate between halothane and isoflurane. Mechanism parallels other volatile anesthetics (GABA-A, K2P, glycine, NMDA modulation). The principal clinical limitation is dose-dependent generation of high-amplitude epileptiform activity on electroencephalography, particularly at end-tidal concentrations above 2.5 percent and during hypocapnia, with occasional clinical seizures during deep anesthesia. The mechanism of enflurane epileptogenesis is incompletely characterized but appears to involve thalamocortical disinhibition at concentrations where cortical inhibition exceeds cortical excitatory tone. This electrophysiological profile contraindicates enflurane in patients with seizure disorders and contributed substantially to its displacement by isoflurane, the structural isomer with similar clinical profile but absent the epileptiform signal. Hepatic metabolism is approximately 2 to 5 percent (intermediate between halothane and isoflurane); fluoride generation is sufficient to raise plasma concentrations into the historically nephrotoxic range during very prolonged exposures. Cardiovascular effects include modest myocardial depression and dose-dependent vasodilation. Clinical use of enflurane has nearly disappeared in developed economies; it remains available as a research tool for halogenated ether structure-activity studies.

3. Mechanism of Action

Standard volatile profile (GABA-A, K2P, glycine, NMDA) with additional dose-dependent epileptiform EEG activity attributed to thalamocortical disinhibition at deep anesthetic 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. 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 1.68 percent in oxygen at age 40; clinical maintenance 1.0 to 2.0 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. Virtue RW, Lund LO. A new ether-type general anesthetic agent: enflurane. Anesthesiology 1968.
2. Neigh JL, et al. The electroencephalographic pattern during anesthesia with Ethrane. Anesthesiology 1971.
3. Mazze RI, et al. Renal toxicity of enflurane. Anesthesiology 1977.

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