**Etomidate**

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**Class:** Carboxylated imidazole-containing hypnotic and anesthetic compound, unrelated to any other anesthetic drug.

**Structure:**

(R)-(+)ethyl-1-(1-phenylethyl)-1H-imidazole-5-carboxylate sulphate

**Commercial Preparation:**

1. Etomidate Injection is a sterile, nonpyrogenic solution containing 2mg/ml etomidate.
2. Etomidate formulations for clinical use contain the purified R(+) enantiomer, which is 5 times more potent than S(-) isomer.
3. Imidazole nucleus renders it water soluble at an acidic pH (but not physiologic pH) and lipid soluble at physiological pH.
4. Etomidate has a pKa of 4.2 and is very hydrophobic at physiologic pH. To increase solubility, it is formulated as a 0.2% solution either in 35% propylene glycol (Amidate; Hospira, Inc., Lake Forest, Illinois, USA) or in lipid emulsion (Etomidate-Lipuro; B. Braun, Melsungen, Germany). Formulations in cyclodextrins have also been developed.
5. Etomidate-® Lipuro: **Composition**
   1 ml emulsion for injection contains Etomidate 2 mg
   Excipients: Soya-bean oil, medium-chain triglycerides, glycerol, egg lecithin, sodium oleate, water for injections.
6. Original preparation containing propylene glycol produces pain on injection due to pH (6.9) and high osmolality (4640mOsm/L).
7. Fat emulsion formulation almost does not produce pain on injection.
8. Oral preparation for transmucosal delivery for dose dependent sedation has been prepared.
9. The pH is 6.0 (4.0 to 7.0).
10. It can be mixed with other anaesthetic drugs like neuromuscular blockers, vasoactive drugs, lidocaine without precipitation.
Etomidate

History:

1. The first report on etomidate was published in 1965 as one of several dozen arylalkyl imidazole-5-carboxylate esters synthesized by Janssen Pharmaceuticals (a division of Ortho-McNeil-Jannsen Pharmaceuticals, Titusville, New Jersey, USA). Initially developed as anti-fungal agents, the potent hypnotic activity of several compounds was observed during animal testing, and several compounds, including etomidate, appeared significantly safer than barbiturates.

2. It was introduced as an intravenous agent in 1972 in Europe and in 1983 in United States.

Mechanism of action:

- Structurally unrelated to other currently available IV anaesthetics.

- It binds directly to a specific site at GABA\(_A\) receptor and enhances the affinity of the inhibitory neurotransmitter (GABA) for these receptors, thus producing CNS depression—from light sleep to deep coma—depending on the dosage.

- Substantial changes on the EEG appear to occur following induction doses. The EEG changes are indicative of the various stages of anaesthesia and appear to be similar to those occurring following induction of anaesthesia with barbiturates.

Pharmacokinetics:

1. Molecular weight— 342.36kD

2. pKa— 4.2

3. Absorption: Intravenous: Predictable, transmucosal: good

4. Volume of distribution at steady-state (V\(_d\)): large, 2-4.5 L/kg (considerable tissue uptake)

5. Protein binding: 76% mainly to albumin, independent of plasma concentration of drug. Decrease in albumin level results in increase in unbound, active fraction of etomidate in plasma.

6. Onset of action: Following IV administration, rapid onset of action (loss of consciousness) one arm- brain circulation time. Moderate lipid solubility and its existence as weak base (pK 4.2, pH 8.2, 99% unionized at physiologic pH) contribute to its rapid onset, and its redistribution in body.

   - Peak effect: within 1 minute
Etomidate

- **Duration**: Dose dependent. Following IV administration of average doses (0.3 mg/kg), duration of hypnosis is short (about 3–5 minutes). Recovery from anaesthesia is at least as fast as with thiopental, but slower than that associated with propofol.

7. **Plasma Concentrations of drug for**:
   - Maintenance of anaesthesia: 300-500ng/ml
   - Sedation: 150-300ng/ml
   - Awakening: 150-250ng/ml

8. **Distribution: Three compartment phase model after intravenous injection**
   - Initial distribution half life: 2.7 minutes
   - Redistribution half life: 29 minutes
   - Elimination half life: 2.9-5.3 hours

9. **Metabolism**:
   - Site of metabolism: Liver
   - Enzymes: Hepatic microsomal enzyme and plasma esterase
   - Rapidly metabolised by hydrolysis (of ethyl ester side chain to its carboxylic acid ester), and N dealkylation to water soluble, pharmacologically inactive compound.
   - Less than 3% of un-metabolised drug is excreted in urine
   - 85% of metabolised drug is excreted through kidney while 15% metabolised drug is excreted through bile.
   - Elimination half life: short 2-5 hours
   - Context sensitive half life is less likely to be increased by continuous infusion as compared to thiopentone.
   - Clearance by liver (High): 18-25ml/kg/min
   - Hepatic extraction ratio: 0.5±0.9

**Uses**

1. **Induction of anaesthesia**
   - a. Useful in unstable cardiovascular patients
   - b. Dose @ 0.2-0.6mg/kg body wt

2. **Maintenance of anaesthesia**
   - a. 10µg/kg/min IV with N₂O and an opiate

3. **Sedation and analgesia**: for limited period only

4. **To decrease duration of seizure during Electroconvulsive therapy**

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**Contraindications:**

- Known hypersensitivity to etomidate.

**Pharmacodynamics:**

1. Central Nervous System:
   a. Dose dependent CNS depression
   b. Potent direct cerebral vasoconstriction: decreases CBF and CMRO\(_2\) by 35-45%
   c. Decrease in ICP while Cerebral Perfusion Pressure is maintained (as Mean BP is maintained)
   d. Seizure like EEG changes: caution in patients with history of seizure (focal history)
   e. Has anticonvulsant effect and used for termination of status epilepticus.
   f. Involuntary myoclonus movements are common during the induction period due to alteration in balance between inhibitory and excitatory influence on thalamocortical tract. The frequency of this myoclonus like activity can be reduced with prior administration of opioids.
   g. Analgesia is not produced by the drug.

2. Cardiovascular System:
   a. @ dose 0.3mg/kg cardiovascular stable, minimal changes in HR, stroke volume or cardiac output whereas mean BP may decrease up to 15% because of decreases in SVR.
   b. In Acute hypovolemic patient, there may be profound hypotension.
   c. Myocardial depressant effects are minimal at anaesthetic dose

3. Respiratory System:
   a. Respiratory depression: present but less than propofol and thiopentone.
   b. Decrease in tidal volume is compensated by increase in respiratory rate. The respiratory depression is transient lasting for 3-5 minutes. Apnoea is not so common at usual dose.
   c. The most characteristic effect of intravenous Etomidate on the respiratory system is a slight elevation in arterial carbon dioxide tension (PaCO\(_2\)).
   d. Depressed response of respiratory centre to CO\(_2\)
   e. Bronchodilator properties present

4. Liver: Minimal decrease in hepatic blood flow, No post operative liver dysfunction
5. Kidney: Minimal decrease in RBF
6. GIT: No effect
7. NM Junction: No Direct action
8. Eye: Decrease in IOP similar to thiopentone.
9. Pregnant Uterus:
   a. Etomidate has no effect on uterine muscle tone.
   b. It crosses placenta

Precautions to Consider:

1. Carcinogenesis, Mutagenesis, Impairment of Fertility
   - No carcinogenesis or mutagenesis studies have been carried out on Etomidate.
   - Animal studies did not showed impairment of fertility in male and female.

2. Pregnancy
   - Category C drug
   - Etomidate has been shown to have an embryocidal effect in rats when given in doses 1 and 4 times the human dose. There are no adequate and well-controlled studies in pregnant women.
   - *Etomidate should be used during pregnancy only if the potential benefit justifies the potential risks to the foetus.*
   - Etomidate has not been shown to be teratogenic in animals.

3. Labour and Delivery
   - There are insufficient data to support use of intravenous Etomidate in obstetrics, including Caesarean section deliveries. Therefore, such use is not recommended.

4. Nursing Mothers
   - It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Etomidate is administered to a nursing mother.
5. **Geriatric Patients**
   - Geriatric patients may require lower dosages than younger patients because of pharmacokinetic differences. Elderly have smaller Volume of distribution and decreased clearance of drug.

6. **Paediatric patients**
   - Safety and efficacy of etomidate for induction anaesthesia or maintenance anaesthesia (to supplement subpotent aesthetic agents during surgical procedures) in children <10 years of age have not been established.

7. **Cirrhosis**
   - In cirrhotic patients volume of distribution is doubled while clearance remains normal, thus elimination half life is twice the normal.

8. **Renal Impairment**
   - Metabolites of etomidate are substantially excreted by the kidneys. The risk of severe adverse reactions may be increased in patients with impaired renal function

9. **Plasma Cortisol Levels**
   - Induction doses of Etomidate have been associated with reduction in plasma cortisol and aldosterone concentrations. These have not been associated with changes in vital signs or evidence of increased mortality; however, where concern exists for patients undergoing severe stress, exogenous replacement should be considered.

**Adverse Reactions:**

1. Transient venous pain on injection:
   - Due to addition of propylene to etomidate
   - Has been eliminated with lipid preparation
   - May be decreased with prior use of lignocaine or opioid or using large vein for injection.

2. Superficial thrombophlebitis

3. Allergic reaction: Low incidence

4. Excitatory effects such as spontaneous movements, such as myoclonus, dystonia and tremors are seen in 50 – 80% patients at the time of induction.
5. Respiratory System: Hyperventilation, hypoventilation, apnoea of short duration (5 to 90 seconds with spontaneous recovery), laryngospasm, hiccup and snoring suggestive of partial upper airway obstruction have been observed in some patients.

6. Circulatory System: Hypertension, hypotension, tachycardia, bradycardia and other arrhythmias have occasionally been observed during induction and maintenance of anaesthesia.

7. Gastrointestinal System: Nausea and vomiting and Hiccups

8. Accidental arterial injection: No major adverse effect.

9. **Transient adrenocortical depression**
   - Dose dependent inhibition of the conversion of cholesterol to cortisol
   - Enzyme inhibited: 11-beta-hydroxylase
   - Enzyme inhibition lasts for 4-8 hours after induction dose.
   - This depression is clinically more significant in critically ill patients or patients receiving prolonged etomidate infusion.
   - However, even a single dose may produce significant adrenal depression.