Pharmacology of intravenous induction agents

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Intravenous induction agents currently available

- thiopental
- propofol
- etomidate
- *midazolam*
- *ketamine*
Common features of the main intravenous induction agents

• Their target is the GABA-A receptor
Common features of the main intravenous induction agents

Central effects:

• \(\uparrow\) brain oxygen consumption
• \(\uparrow\) cerebral blood flow
  • \(\uparrow\) ICP
  • The consequence on CPP depends on MAP
• anticonvulsants, but etomidate and propofol may elicit myoclonic movements
• No analgesic properties
Common features of the main intravenous induction agents

Respiratory effects:
  • depression of the respiratory command centres
    • Apnoea is frequent after a bolus dose
  • They maintain the pulmonary hypoxic vasoconstriction

BUT
  • Propofol is the only one to depress the pharyngeal and glottic reflexes and may be used (with an opioid) for intubation without NMBA
  • Propofol, not thiopental, is a bronchodilator and may be used in asthmatic patients
## Hemodynamic consequences of intravenous induction agents administration

<table>
<thead>
<tr>
<th></th>
<th>Thiopental</th>
<th>Propofol</th>
<th>Etomidate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inotropic effect</td>
<td>↓↓</td>
<td>≃</td>
<td>≃</td>
</tr>
<tr>
<td>dilation</td>
<td>venous</td>
<td>Arterial and venous</td>
<td>≃</td>
</tr>
<tr>
<td>Cardiac output</td>
<td>↓</td>
<td>↓</td>
<td>≃</td>
</tr>
<tr>
<td>AP</td>
<td>↓</td>
<td>↓↓</td>
<td>≃</td>
</tr>
<tr>
<td>HR</td>
<td>↑</td>
<td>≃</td>
<td>≃</td>
</tr>
<tr>
<td>Oxygen consumption</td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td></td>
<td>Avoid if ischemic heart disease or hypovolemia</td>
<td>Avoid if hypovolemia</td>
<td>Hemodynamic effects are minimal even in cardiac failure</td>
</tr>
</tbody>
</table>
Inotropic effects of propofol, thiopental, midazolam, etomidate and ketamine on isolated human atrial muscle

At clinically relevant concentrations, etomidate has no inotropic negative effect, contrary to thiopental. Ketamine has a small inotropic negative effect, which is usually hidden by a stimulation of the sympathetic nervous system.

Gelissen, Harry P et al, Anesthesiology 1996
Influence of hemorrhagic shock on Propofol

Experimental shock in swine. Animals then received propofol 200µg.kg\(^{-1}\).min\(^{-1}\) during 10 min.

*Johnson K et al, Anesthesiology 2003*
Propofol in elderly patients: the hemodynamic effect is enhanced and delayed

Blood / effect site equilibration half life

30 yrs : 5.68 min
80 yrs : 10.22 min

Kazama, Anesthesiology 1999
Thiopental: Chemical properties

- 1934
- Barbiturate with a sulfur ion
- pKa 7.6 → mainly non-ionized at physiological pH
- The salts are water-soluble
- Presented as a powder to dissolve in water or saline NOT lactated Ringer
- Solution very alkaline (pH >10) →
  - Tissue damage if extravasation
  - Precipitates with acids (NMBA)
  - Bacteriostatic
- Recommended dilution; 2.5% in adults, 1% in children
Thiopental: pharmacokinetics

• Binding to albumin (80%) saturable at high concentrations (bolus effect)

• Rapid initial transfert to the effect site and distribution ➔ a single bolus of 4 to 7 mg/kg has a rapid and short lasting effect

• Low metabolic clearance # 250 ml/min
  • oxidation by P450 cytochromes (E ~ 15%)
  • This elimination is saturable
  • No active metabolite

• High cumulative potential +++ if iterative boluses or infusion

• Cannot be used for maintenance of anaesthesia
Thiopental: unwanted effects

• contra-indicated in patients with acute intermittent or variegata porphyria
• Tissue necrosis if extravasation
• Intra-arterial administration leads to spasm +++ and downstream ischemia
• Not to be used in ischemic heart disease or hypovolemia
• Reduce the doses +++ and titrate in the elderly
• Do not use with a laryngeal mask
Propofol: Chemical properties

- Propofol
  - PM = 178
  - Lipid-soluble
  - pKa = 11
  - Bound to albumin # 98%

- Lipid emulsion
  - Lipid emulsion 10 or 20 mg/ml
  - Isotonic – neutral pH
  - Allows bacterial growth (precautions for use, associated with EDTA in many European countries)
  - Do not freeze
  - Do not dilute
  - Do not use a bacterial filter
Propofol: pharmacokinetics

- Rapid and major distribution
  - $t_{1/2\alpha} \approx 3$ min
  - $V_{ss} \approx 200$ l.
- Metabolic clearance $\approx 2$ l/min
  - Mainly conjugated
  - No active metabolite
  - Extra-hepatic metabolic sites
  - Flow dependent clearance
- No accumulation despite the $V_{ss}$.
- Well suited to maintenance of anaesthesia
- May be administered as a TCI
- Usual dose = 2 to 2.5 mg/kg
Other propofol effects

- Anti-emetic properties
- Anti-oxidant (structural analogue of vitamin E)
- May be used in patients at risk of malignant hyperthermia
- May be used in patients with asymptomatic porphyrias
Propofol unwanted effects

• **Pain on injection**
  • Due to the drug, not the solvent
  • May be reduced by the simultaneous administration of lidocaine (optimal lidocaine dose 30mg) (Cochrane review 2016)

• **Transmission of pathogenic agents.**
  • Several clusters of infections published
  • Always linked to inappropriate handling
  • Recommendations have been published
  • A conservative agent is frequently added

• **Use with caution if at all in hypovolemic patients**
New propofol formulations

Fospropofol

- Phosphate pro-drug for propofol
- Water soluble, no pain on injection
- Requires conversion to propofol before being active (Usual dose = 6.5 mg/kg).
- As a result induction time is longer
- Mainly used for sedation (digestive endoscopy).
Etomidate: chemical properties

- Carboxy-imidazole
- PM = 244
- pKa = 4.24
- No water-soluble \( \Rightarrow \) requires a solvent (propylene glycol or lipid emulsion)
Etomidate pharmacokinetics

- Rapid and extensive distribution
  - $t_{1/2\alpha} \approx 3$ min
  - $V_{ss} \approx 300$ l.
- Metabolic clearance $\approx 1.2$ l/min $\approx$ hepatic blood flow
  - Hydrolysis by hepatic esterases
  - No active metabolite
- Usual dose $= 0.3$ mg/kg
Etomidate unwanted effects

• **Pain on injection**+++ with 20% of **postoperative thrombophlebitis** (solvent ++)
• **Myoclonus** frequent in non premedicated young patients
• **Nausea and vomiting** (30 to 40% of cases, more if associated to an opioid)
• **Inhibition of cortisol secretion**
  • Can be used only for induction of anaesthesia

    Not a pleasant drug in young fit patients, but irreplaceable in cardiac failure or hemodynamically compromised patients.
# Etomidate: pain on injection

<table>
<thead>
<tr>
<th>Study</th>
<th>Etomidate-lipuro</th>
<th>Etomidate-PG</th>
<th>Propofol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suttman 1989</td>
<td>0</td>
<td>50%</td>
<td></td>
</tr>
<tr>
<td>Kulla 1993</td>
<td>14%</td>
<td>78%</td>
<td></td>
</tr>
<tr>
<td>Mayer 1996</td>
<td>2%</td>
<td></td>
<td>50%</td>
</tr>
<tr>
<td>Doenicke 1999</td>
<td>10%</td>
<td>90%</td>
<td></td>
</tr>
<tr>
<td>Nyman 2006 (children)</td>
<td>5%</td>
<td></td>
<td>48%</td>
</tr>
</tbody>
</table>
Etomidale without adrenocortical impairment?

New molecules are currently under investigation. No human studies yet.

- **MOC-etomidate**: the kinetic solution. Ultra-rapid metabolism
MOC-etomidate: THE solution?

- MOC-etomidate: ultra-rapid metabolism and low potency → massive doses need be injected to induce and maintain hypnotic state → accumulation of metabolites

![Ester group](image)

<table>
<thead>
<tr>
<th></th>
<th>ED50 (mg/kg)</th>
<th>T1/2 (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etomidate</td>
<td>0.53</td>
<td>99</td>
</tr>
<tr>
<td>MOC-etomidate</td>
<td>5.3</td>
<td>0.41</td>
</tr>
<tr>
<td>DMMM</td>
<td>9.6</td>
<td>8.7</td>
</tr>
<tr>
<td>CPMM</td>
<td>0.69</td>
<td>0.57</td>
</tr>
</tbody>
</table>

Husain Anesthesiology 2012
Etomidale without adrenocortical impairment?

- Carbo-etomidate: the dynamic solution. Pyrrolic derivative of etomidate designed to have a reduced affinity to 11-β-hydroxylase.

*Cotten Anesthesiology 2010

*Shanmugasundararaj, A&A 2013*
Remimazolam

- Hydrolysis by tissular esterases
- Benzodiazepine

Wiltshire A&A 2012
Rapid induction: which agent?

Fraction du pic de conc - temps (min)

- midazolam
- étomidate
- propofol
- thiopental
Rapid induction: which agent?

![Graph showing the peak concentration times for different agents with labels midazolam, étomidate, propofol, and thiopental.](image-url)
## propofol / thiopental

<table>
<thead>
<tr>
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<th>Propofol</th>
<th>Thiopental</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Equipotent doses (ED\textsubscript{95})</strong></td>
<td>2.22 mg/kg</td>
<td>3.56 mg/kg</td>
</tr>
<tr>
<td><strong>Hemodynamic effects</strong></td>
<td>RVS ~FC ~I</td>
<td>RVS AFC I</td>
</tr>
<tr>
<td><strong>Induction time (bolus)</strong></td>
<td>45 sec.</td>
<td>30 sec.</td>
</tr>
<tr>
<td><strong>Recovery time</strong></td>
<td>~5 min</td>
<td>~10 min</td>
</tr>
<tr>
<td><strong>Quality of recovery</strong></td>
<td>+++</td>
<td>±</td>
</tr>
<tr>
<td><strong>Incidence of apnoeas</strong></td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td><strong>Pain on injection</strong></td>
<td>10 - 50%</td>
<td>~0</td>
</tr>
</tbody>
</table>
What do patients fear most in general anaesthesia?

1) Pain at operative site
2) PONV
4) Preoperative anxiety
5) Discomfort at placing of venous line
6) Shivering
7) Pain at propofol injection
8) Sore throat
9) Several venous puncture to place line
10) Post-anaesthesia fatigue

Macario, Anesth Analg, 1999
Conclusion: which induction agent?

- **Thiopental**: induction of anaesthesia expected to last over 90min if volatiles are considered for maintenance, rapid induction

- **Propofol**:
  - Induction and maintenance of anaesthesia; TCI
  - Short procedures, ambulatory anaesthesia,
  - Laryngeal mask
  - Per-operative sedation, TCI; PCS

- **Etomidate**: induction of anaesthesia in patients who will not tolerate vasodilation or with compromised myocardium.

- **Midazolam**: cardiac surgery?

- **Ketamine**: patients with multiple allergies? septic shock?