The Development of Propofol and its use in Pregnancy

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Former employee of ICI, AstraZeneca
Main Topics

- How I became involved in anaesthetic research
- Discovery of anaesthetic properties of propofol
- Search for an improved formulation
- Use in pregnancy
Corrieccravie, Isle of Arran
Anaesthetics Project Team Objectives, 1972

- Search for new anaesthetic agents
- Evaluate new methods to study anaesthetic drugs
TARGET PRODUCT PROFILE

- A short acting iv anaesthetic
  - Rapid onset
  - Good quality of anaesthesia - freedom from excitatory effects
  - Acceptable haemodynamic and respiratory effects
  - Rapid metabolism
Drugs for test provided by Project Team chemists

- Chemical modification of known anaesthetic agents
- Random selection of compounds from ICI compound collection
‘CATCH 22’ Problem

- Water solubility is required to achieve an aqueous solution for i.v. Injection

- High lipid solubility for anaesthetic potency leads to poor water solubility
Formulation of Propanidid in Cremophor EL

Cremophor Micelle has a lipophilic core and polyoxyethylene side chains which provide water solubility.

Water insoluble agent

Scholtan & Lie, 1966
Lead compound

- 2,6 diethylphenol
- Anaesthetic but low potency
**Preparation**
10 mg und 1% nembutal. Dünnt mit destilliertem Wasser

**Yellow solution**
IV 1 ml sec

<table>
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<th>Dose</th>
<th>Vol/hl</th>
<th>Wt</th>
<th>Duration of SP</th>
<th>Av</th>
<th>No. In</th>
<th>SP</th>
<th>Depth</th>
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</table>

**Animal**
PB 50 1975 (15.5.73) 15.2 g

**I.V. Anaesthetic Screening Test**

**Date** 23.5.73
2, 6 – diisopropylphenol (ICI 35,868) 
Propofol is a hindered phenol 
Aqueous solubility 0.2 % (2mg/ml)
SECONDARY TESTS

- Evaluation of quality of anaesthesia in rabbits
- Speed of onset in mice
Influence of 2,6 substitutions on hypnotic potency and induction time

<table>
<thead>
<tr>
<th>2,6 substitution</th>
<th>Median Hypnotic Dose (mg/kg)</th>
<th>Induction Time (s)</th>
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<td>C₂H₅</td>
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<td>5.4</td>
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<td>C₃H₇</td>
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<td>\text{CH(CH₃)₂}</td>
<td>7.5</td>
<td>4.6</td>
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<tr>
<td>\text{CH(CH₃)C₂H₅}</td>
<td>4.8</td>
<td>8.8</td>
</tr>
<tr>
<td>\text{C(CH₃)₃}</td>
<td>80 - 100</td>
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</tr>
<tr>
<td>Thiopentone</td>
<td>20-25</td>
<td>3.6</td>
</tr>
</tbody>
</table>
Sleeping Time Following Repeated Bolus Doses in Mice

![Graph showing sleeping time in minutes following repeated bolus doses of Propofol and Thiopentone. The x-axis represents the number of doses (1 to 10), and the y-axis represents sleeping time in minutes (0 to 200). The graph indicates that Propofol maintains a consistent sleeping time, whereas Thiopentone shows a significant increase in sleeping time with each additional dose.](image-url)
Testing Recovery of Coordination
Recovery of Coordination in Mice

![Graph showing recovery times for sleeping, interval to walking, and interval to balancing for mice under Propofol and Thiopentone.

- Sleeping Time (min)
- Interval to Walking (min)
- Interval to Balancing (min)

Propofol
Thiopentone

Graph Title: Recovery of Coordination in Mice

Graph X-axis: Time (min)
Graph Y-axis: Time (min)
Tests to predict avoidance of known undesirable effects of other agents

- Tissue damage with intra-arterial or peri-venous injection
- Porphyria
- Malignant hyperthermia
- Adrenocortical suppression
EFFECTS OF DIPRIVAN, ETOMIDATE AND THIOPENTONE ON CORTISOL PRODUCTION IN VITRO: GUINEA-PIG ADRENAL CELLS

Graph showing the effects of Etomidate, Thiopentone, and Diprivan on cortisol production in guinea-pig adrenal cells. The x-axis represents the concentration of anaesthetic (mol/l), and the y-axis represents the inhibition (%). Mean values ± SD, n = 6.
THE SELECTION OF PROPOFOL

- Primary Screen in Mice  5000 Tested
- Quality of Anaesthesia  300 Tested
- Detailed Pharmacology  30 Tested
- Candidate Drug  1
1% Propofol in 16% Cremophor EL
The search for an improved formulation

- Cremophor EL suspected of contributing to anaphylactoid reactions to ‘Epontol’ and ‘Althesin’
- No adverse effect of Cremophor in conventional models of anaphylaxis
- Dogs sensitive to Cremophor – histamine release and marked hypotension
The Effect of Chemophor EL on Arterial Blood Pressure in a Dog.

14 kg dog. 3.6 ml 16% cremophor EL i.v. given between the arrows.
Hypersensitivity reaction to Cremophor EL in pig model

- Requires exposure 7-14 days previously
- Histamine release
- Margination of polymorphs indicative of complement activation and release of chemotactic anaphylatoxin C5a
Repeated injection of Propanidid in mini-pig

<table>
<thead>
<tr>
<th>Agent</th>
<th>Vehicle</th>
<th>Adverse response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propanidid as ‘Epontol’</td>
<td>Cremophor EL</td>
<td>90%</td>
</tr>
<tr>
<td>Propanidid</td>
<td>Alcohol/propylene glycol</td>
<td>0%</td>
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</table>
Histamine concentration in mini-pigs on a second administration of propofol.
PROPOFOL DEVELOPMENT TIME SCALE

- 1973 Anaesthetic activity discovered
- 1986 First commercial launches for induction and short term maintenance of anaesthesia
Extension of indications planned

- Long term maintenance of anaesthesia
- Sedation of ventilated ICU patients
- Use in children
- Use in obstetrics
- Use for conscious sedation
- Use of 2% formulation
- Administration by ‘Diprifusor’ TCI system
Animal studies relevant to use in pregnancy

- Full teratology studies (i.v.) in rats and rabbits
- Fertility and general reproductive performance study (i.v.) in rats
- Dominant lethal study (i.v.) in rats
- Peri- and post-natal study (i.v.) in rats
- Mutagenicity tests
Results of animal and in-vitro studies with propofol

- No evidence of any teratogenic effect
- No impairment of fertility
- No evidence of mutagenicity
- Some maternal deaths in rats and rabbits and decreased pup survival during the lactating period in dams treated with 15mg/kg/day.
- These deaths considered to result from the pharmacological effect of high doses of propofol in the mothers.

- Group 1 Thiopentone 5 mg/kg (PBW)
- Group 2 Propofol 2.8 mg/kg (PBW)
- Group 2 Spontaneous vaginal delivery without analgesia

- Suxamethonium and 50% N₂O/O₂ until delivery. I-D interval 11 min
Celleno et al. (1989)

- Apgar scores in propofol group significantly lower than in thiopentone group at 1 and 5 min (P < 0.05, Mann Whitney U test))
- Muscular hypotonus in 25% of infants in propofol group at 5 min
- Minor changes in ENNS at 1hr but not at 4hr
# Apgar Scores

## Celleno et al Apgar Scores

<table>
<thead>
<tr>
<th>Apgar Score</th>
<th>Control</th>
<th>Thiopentone</th>
<th>Propofol</th>
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</thead>
<tbody>
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<td>2</td>
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<td>7</td>
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ICI decision to contraindicate use in obstetrics

- Results of Celleno study
- Slow recruitment to other studies in obstetrics
- Widespread use of neuraxial anaesthesia
- No clear advantage over thiopentone
- Ready availability of thiopentone
Pregnancy
The safety of Diprivan 1% during pregnancy has not been established. Diprivan 1% should not be given to pregnant women except when absolutely necessary.

Obstetrics
Diprivan 1% crosses the placenta and can cause neonatal depression. It should not be used for obstetric anaesthesia unless clearly necessary.
Studies demonstrating no difference in Apgar scores between propofol and thiopentone

<table>
<thead>
<tr>
<th>Study</th>
<th>Propofol dose (mg/kg)</th>
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<tbody>
<tr>
<td>Moore et al, 1989</td>
<td>2.15</td>
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<tr>
<td>Valtonen et al, 1989</td>
<td>2.5</td>
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<td>Gin et al, 1990</td>
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</tr>
<tr>
<td>Yau et al, 1991</td>
<td>2.0</td>
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<tr>
<td>Gin et al, 1993</td>
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</table>
Propofol infusion for Caesarian section, Gregory et al, 1990

- Propofol 2 mg/kg, 6 mg/kg/h + 50% N₂O
- Propofol 2 mg/kg, 9 mg/kg/h + 50% N₂O
- Thiopentone 4 mg/kg, enflurane 1% + 50% N₂O

- Apgar scores similar in all groups but NACS scores at 2hr slightly lower in high infusion group
Favouring use of thiopental (Lucas and Yentis 2015)

- Well known to generations of anaesthetists
- Relatively cardiostable
- Longer lasting than propofol – less risk of awareness
- More known about effects on foetus than propofol
Favouring use of propofol (Lucas and Yentis 2015)

- Junior anaesthetists more familiar with propofol
- Evidence of overdosage of thiopentone (MBRRACE report)
- Evidence of underdosage of thiopental (NAP5)
- No premixing required
- Risk of thiopental-antibiotic syringe swap
- Thiopental in short supply
NAP5 suggestions

- Need to reinvigorate research on general anaesthesia in obstetrics
- Appropriate dose and method of delivery of propofol
- Effect on the compromised mother and foetus
- Safe minimum FiO₂
- Optimum timing and dosing of opioids
SPCs for generic preparations of propofol

- Sandoz, Hospira, and B Braun (Propofol Lipuro) follow Diprivan labelling.

- Others add: “High doses (more than 2.5 mg/kg for induction or 6 mg/kg/h for maintenance of anaesthesia) should be avoided.”
Maternal anaesthesia and foetal neurodevelopment

- Most anaesthetics in sufficient doses lead to neurodegeneration in foetal and newborn rats
- Mixed evidence from cohort studies that young children exposed to anaesthesia can have an increased risk of poor neurodevelopmental outcome.
- Prospective studies underway: GAS, PANDA, MASK
Anesthesia for non-obstetric surgery.

Cheek T and Baird E. Clin Obst and Gyn 2009,52: 535

- Until further research defines more clearly the influence of anaesthetic agents on human neuronal development, the mitigation of pain and stress during surgery should remain the primary goals of pediatric and obstetric anesthesia
- Avoid prolonged or repeated exposure when possible