Propofol

Chemical Structure

2,6 diisopropylphenol is an alkylphenol; it is a phenol ring with two isopropyl groups. Chemically, it is a weak organic acid. The pKa is 11, so at pH 7.4 most of the drug is fat-soluble. Thus, 90% is not ionized at a physiologic pH.

The vial contains

- 1% propofol (10mg/ml)
- 10% soybean oil
- 1.2% purified egg phospholipid, a yolk component
  - People are usually not allergic to this; egg allergy is usually an allergy to egg albumin
- 2.25% glycerol, to adjust tonicity
- Sodium hydroxide is also present to keep the pH between 6 and 8.5.
- Sodium EDTA (Ethylenediaminetetraacetic acid) – as an antimicrobial additive, a minute amount.

Chemical Relatives

Alkylphenols are a diverse group. The only chemically related one is fospropofol, which is just propofol with a phosphate group substituted onto it. The whole point is that fospropofol is a water-soluble pro-drug, with various advantages of increased water solubility like for example no pain on injection.

Administration and Absorption

Propofol has zero oral bioavailability. It is very bitter-tasting. It is invariably given intravenously. It is 98% protein bound. Thus, it has the highest volume of distribution of any induction agent.

Distribution of an induction dose of propofol

Onset of action is one arm-brain circulation.

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The propofol bolus doesn’t spend very long in the plasma compartment. It distributes rapidly to all fatty tissues. Usefully, that includes the brain.

Propofol penetrates the placenta, but is usually held to be harmless for the foetus.

Bolus Volume of Distribution  = 4.1L/Kg
Steady state volume of distribution = 2-10 L/Kg

Bolus Half life = 120 seconds
Half Life from Steady State = 5-12 hours

From "Goodman & Gilman’s The Pharmacological Basis of Therapeutics" 11th ed. by Brunton et al. and "Basic & Clinical Pharmacology" 11th ed. By Katzung et al. as well as a chapter devoted to propofol in the excellent "Clinical Anaesthesiology" by Morgan, McAneny and Murray. There is a good article about propofol clearance. Furthermore, the ever-so-helpful AstraZeneca people have a PI document in pdf for you to read. Propofol infusion syndrome is well covered by Kam (Yes, THAT Kam)
**Distribution of a propofol infusion**

Context-sensitive half-life after 3 hours of infusion is 10 minutes; After 8 hours that rises to 30 minutes. And so on.
The context-sensitive half-life increases with prolonged infusions, as a massive cache of propofol builds up inside fat patients.

**Metabolism and Clearance**

**Metabolism** is by glucuronide and sulphate conjugation, which happens mainly in the liver. However, it seems the clearance rate exceeds hepatic blood flow, so there must be some extrahepatic site of metabolism. Furthermore, even people with moderate cirrhosis don’t seem to have much of a problem metabolizing normal quantities of propofol.

**Clearance rate** is rapid, 30-60ml/kg/min. That’s about 10 times faster than thiopentone. CYP450 is the main enzyme system involved in this.

40% is metabolised to a glucuronide
60% is metabolised to a quinol, which is then metabolised into a glucuronide and a sulfate.

All the metabolites are inactive and excreted renally, which can give the urine a healthy green tinge.

Clearance of propofol is decreased in neonates and the elderly.
**Mechanism of Action**

Propofol activates GABA_A channels

Propofol opens these chloride channels and causes chloride to enter the cell. This brings the cell closer to the "reversal potential" for chloride, which is below the depolarization threshold. Thus, the membrane comes to be hyperpolarized.

**Effects of propofol**

Duh, it’s a general anaesthetic.

Propofol also has numerous non-sedation-related effects:

- **Antiemetic** – perhaps due to a dopamine (D2) receptor antagonism.
- **Antihistamine, antipruritic**
- **Anticonvulsant?**.. some choreiform movements have been observed, with opisthotonos. That’s all probably due to a subcortical glycine antagonism. Propofol does antagonize tonic-clonic seizures.
- **Cerebral blood flow is decreased**: this could be good or bad.
- **Dose dependent respiratory depression** – more than thiopentone
  - Decreased tidal volume and increased respiratory rate
  - Impaired or even completely abolished response to hypoxia and hypercapnea
- **Bronchodilation**
- **Depressed laryngeal reflex**

**SYMPATHOLYTIC EFFECTS:**

- Impaired or completely abolished the arterial baroreflex response to hypotension;
- This means, a shocked patient who is compensating for their shock will stop compensating, and crash hideously on induction.

- **Dose-dependent decreased heart rate and decreased cardiac output**
- **Dose-dependent vasodilation and hypotension** – more than thiopentone

- **Decreased hepatic blood flow**
- **Green urine, as well as potentially green hair:** due to the phenols

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Indications for Use
- For induction of anaesthesia:
  - The baseline dose is 2-3mg per Kg. This textbook number differs wildly from practical experience, because of massive individual variability.

Contraindications
- Hemodynamic instability, poor cardiac output, or shock.
- Allergy to any of the ampoule contents
- Ridiculously high serum triglycerides
- Very high intracranial pressure

Interactions
- Some say, co-induction with midazolam and propofol has a synergistic effect.
- Some also say that with fentanyl or alfentanil, the opisthotonic rigidity is worse.

Chronic Toxicity: Propofol Infusion Syndrome (PRIS)
- This tends to happen after about 48 hours of propofol infusion, at over 4mg/kg/hr. (around 28ml/hr of straight propofol, for a normal 70kg male)
  - The mechanism is likely the inhibition by propofol of coenzyme Q and Cytochrome C;
  - This results in a failure of the electron transport chain, and thus the failure of ATP production
  - Furthermore, fatty acid metabolism is impaired: the conversion of FFAs to acetyl-CoA is blocked, and again, no ATP is produced. AND on top of that you get unused free fatty acids acidifying the bloodstream.
  - PRIS is more common in children
  - The treatment, unsurprisingly, is to stop the propofol.
  - Charcoal hemoperfusion can be used to get rid of the excess fatty acids.

Acute Toxicity and Overdose
- Erm, THESE WOULD BE SEDATION-RELATED.
- One would manage such an event by completing the process of anaesthetic airway control and ventilation.