THE NORTHERN HOSPITAL

PROPOFOL

"The Dream", oil on canvas, 1932, Pablo Picasso

Spare a little candle
Save some light for me
figures up ahead
Moving in the trees
White skin in linen
Perfume on my wrist
And the full moon that hangs over
these dreams in the mist

Darkness on the edge
Shadows where I stand
I search for the time
On a watch with no hands
I want to see you clearly
Come closer than this
But all I remember
Are the dreams in the mist

These dreams go on when I close my eyes
Every second of the night I live another life
These dreams that sleep when it's cold outside
Every moment I'm awake the further I'm away

Is it cloak 'n dagger
Could it be spring or fall
I walk without a cut
Through a stained glass wall
Weaker in my eyesight
The candle in my grip
And words that have no form
Are falling from my lips

These dreams go on when I close my eyes
Every second of the night I live another life
These dreams that sleep when it's cold outside
Every moment I'm awake the further I'm away

There's something out there
I can't resist
I need to hide away from the pain
There's something out there
I can't resist

The sweetest song is silence
That I've ever heard
Funny how your feet
In dreams never touch the earth
In a wood full of princes
Freedom is a kiss

But the prince hides his face
From dreams in the mist

These dreams go on when I close my eyes
Every second of the night I live another life
These dreams that sleep when it's cold outside
Every moment I'm awake the further I'm away

These dreams go on when I close my eyes
Every second of the night I live another life
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Every moment I'm awake the further I'm away

Heart, "These Dreams", 1985.

When we need to hide our patients away from a pain they cannot resist, we can induce in them a deep sleep, whereby for a short while they may live another life. Like a watch without hands they will be oblivious to time, it could be spring or it could be fall. In their dreams though they may pass through a stain glass window- they will not be cut. These dreams may go on and on, but as through a mist only vaguely perceived. More often than not they are of a not unpleasant nature - feet not touching the ground, gliding through the air, enchanted moonlit forests, even freedom with a kiss!

...These dreams go on when I close my eyes,
Every second of the night I live another life...

"Bather in the Forest" oil on canvas, 1883, Paul Merwart

PROPOFOL

Introduction

A 20 ml ampoule of 1% propofol emulsion and a 100 ml bottle for infusion. Propofol is a milky -white anesthetic induction agent - the milk of amnesia".

Propofol (trade name **Diprivan)** is a unique non-barbiturate, short-acting, intravenous sedative - hypnotic - anesthetic agent, widely used in Anesthesia and Emergency Medicine.

It has a number of advantages over the older IV barbiturate induction agent, thiopentone, particularly with regard to rapidity of the onset and offset of action.

It must only be administered by those with the appropriate skills in airway and ventilation management, and only in setting of full availability of resuscitation drugs and equipment.

Propofol is on the World Health Organization's List of Essential Medicines, a list that includes the most effective and safe medicines needed in a health system.

Propofol is also widely used in Veterinary Medicine

History

Propofol was developed in the 1970s by the **British Veterinarian, John B. (Iain) Glen** who was working at ICI (Imperial Chemical Industries) as a researcher. It took him 13 years to develop the agent. In 2018 he was finally recognized for his achievement by being awarded the Lasker prize for clinical research.

Clinical trials in 1977, used a form solubilised in cremophor EL which produced anaphylactic reactions.

In 1986 it was reformulated as an emulsion of a soya oil/propofol mixture in water and it was introduced to clinical practice, in the US in 1989, under the trade name of Diprivan.

Chemistry

Propofol is **2,6-di-isopropylphenol.**

Preparations

Propofol has been referred to as **milk of amnesia** (a play on words of milk of magnesia), because of the milk-like appearance of its intravenous preparation.

Ampoules:

A milky white injectable emulsion as:

- **20 ml ampoule of 200 mg,** (i.e. 1 % solution - 10 mg /ml)
- 50 ml ampoule of 500 mg (i.e. 1 % solution - 10 mg /ml)

The vehicle additives are glycerol, soya oil, sodium hydroxide, egg lecithin, disodium edetate and water for injection.

Propofol is an oil at room temperature, and therefore is formulated for intravenous administration in a lipid emulsion containing soya oil and egg lecithin.

When administered using a y-type infusion set, propofol injectable emulsion has been shown to be compatible with 5% Dextrose, Hartmann's solution, Normal saline and Saline/ dextrose solutions.

Pre-filled syringes:

- 20 mL, 50 mL

Vials:

- 20 mL, 50 mL, 100 mL

Mechanism of Action

The mechanism of action of propofol is poorly defined.

Its main central nervous system depressant action is thought to be via gamma-amino-butyric acid (GABA) A receptors at a site of action other than that of benzodiazepines and barbiturates.

Pharmacodynamics

The majority of pharmacodynamic properties (as well as adverse effects) exhibited by propofol are proportional to the dose or concentration in the blood.

The actions of propofol include:

1. Sedation/ hypnosis for short procedures
2. General anesthesia, (in higher doses)
    - For induction:
        - ♥ Unconsciousness occurs approximately 30 seconds after injection
        - ♥ Recovery from anaesthesia is usually rapid, over a period of 3-5 minutes.
    - For maintenance of anesthesia
3. Anticonvulsant
4. Amnesic effect.

Propofol does **not** possess significant analgesic effects.

Advantages over thiopentone

These include:

- Somewhat less hypotension/ myocardial depression, (but can still be significant)
- Inadvertent Intra-arterial injection does not cause intense pain or vasospasm.
- Allergic reactions are very rare, and much rarer than is the case with thiopentone
- Laryngospasm is less common.
- Relatively greater depression of pharyngeal reflexes, making insertion of LMA easier.

- Propofol has the same onset time as thiopentone but has a quicker *recovery* time (4 to 8 minutes) and does not rely on redistribution for recovery.

- Less "hangover" effects

- Can be given as a continuous infusion without accumulation in the tissues.

Disadvantages compared to thiopentone

- Propofol causes a greater depression of laryngeal reflexes than thiopentone.

Pharmacokinetics

Absorption:

- Propofol is administered undiluted by **IV** bolus or IV infusion

  Onset of action is rapid - approximately 30 seconds

Distribution:

- The pharmacokinetics of propofol follows a three compartment open model with compartments representing:

  - ♥ The plasma
  - ♥ Rapidly equilibrating tissues, (including the CNS)
  - ♥ Slowly equilibrating tissues.

  Following an intravenous bolus dose, there is rapid equilibration between the plasma and the highly perfused tissue of the brain, thus accounting for the rapid onset of anaesthesia.

  Plasma levels initially decline rapidly as a result of both distribution and metabolic clearance.

  The initial (distribution) half-life is between two and four minutes, followed by a rapid elimination phase with a half-life of 30 to 60 minutes and followed by a slower final phase, representative of redistribution of propofol from poorly perfused tissue.

  Accumulation may occur if higher than necessary infusion rates are used.

- Protein binding is high (97 - 99%)

- Propofol rapidly crosses the human placenta and distributes in the fetus

- Propofol is excreted into human breast milk in small amounts.

Metabolism and excretion:

- Propofol undergoes hepatic metabolism to inactive metabolites.

Indications

These include:

1. Sedation for short procedures in the ED
2. Induction and maintenance of anesthesia:
3. Third line agent for control of seizures

Contra-indications/ precautions

These include:

1. Unfasted patients
2. Known hypersensitivity to propofol or its additive components (**soya, egg lecithin**).
3. As with all anaesthetic agents propofol should only be given by those appropriately trained airway management
4. All resuscitation drugs and equipment should be immediately available

Pregnancy:

Propofol is classed as a category C drug with respect tot pregnancy.

Category C drug are those drugs which, owing to their pharmacological effects, have caused or may be suspected of causing harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible. Specialised texts should be consulted for further details.

Propofol rapidly crosses the placenta and distributes in the fetus, but adverse pregnancy outcomes have not been reported.

Maternal use of propofol near term may be associated with respiratory depression in the newborn. However, propofol is considered safe to use in pregnancy.

Breastfeeding:

Small amounts of propofol are excreted into breast milk, but these amounts are unlikely to pose harm to breastfed infants.

Propofol is considered safe to use during breastfeeding.

Adverse Effects

These include:

1. CVS:
    - Hypotension
    - Vasodilation
    - Myocardial depression
    - Transient bradycardia
2. Respiratory:
    - Respiratory depression.
    - Transient apnea also may be seen.

    Brief apnea and respiratory depression requiring ventilatory support is generally more common with propofol than with midazolam/opioid combinations that are also commonly used in procedural sedation.
3. Neurological:
    - Propofol is synergistic with other CNS depressants
    - Occasional neuro-excitatory phenomena
        - ♥ These are mainly seen on induction and emergence
        - ♥ They are myoclonic jerking movements, and not true seizure activity.
    - Occasional transient euphoria/ dysphoria
    - Dreaming (often of a pleasant nature) is uncommon, but has also been reported.
4. Some pain on injection of propofol may occur:
    - Mixing propofol with 1 ml of 1% lignocaine as well as injecting into a larger vein reduces the incidence of pain.
5. Allergic reactions:
    - Allergy to propofol has been reported but this it is rare (1 in 60,000 - far lower than is the case with thiopentone)

- Allergic reactions may also occur to the exipients (soya, egg lecithin).

6. Metabolic:

   - Hyperlipemia:

     ♥ Propofol injection is formulated in an oil-in-water emulsion.

     Elevations in serum triglycerides may occur when propofol is administered for extended periods of time.

     Patients at risk of hyperlipidaemia should be monitored for increases in serum triglycerides or serum turbidity.

7. Propofol related infusion syndrome (**PRIS**):

   Propofol-related Infusion Syndrome is a rare but life-threatening condition characterized by:

   Acute refractory bradycardia (which can progress to asystole) and one or more of:

   - Metabolic acidosis
   - Rhabdomyolysis
   - Hyperlipidaemia
   - Enlarged or fatty liver

   It is often fatal.

   It usually only effects patients undergoing longer term treatment with high doses of propofol.

   See also separate document on Propofol Related Infusion Syndrome (PRIS) (in Toxicology folder).

Dosing

Usual sedation doses for short painful procedures is **1-2 mg/kg IV**

Usual anaesthetic induction dose is **2 - 2.5 mg/kg IV**

Note however that there is a wide variation in the dose required to achieve sedation or unconsciousness; therefore doses should be titrated incrementally.

A small dose of short-acting opioid improves the smoothness of induction and reduces the dose required; however, it potentiates respiratory depression. [3]

Doses for the induction of anesthesia can vary widely in the **critically ill** (typically 20 mg to 200 mg).

In particular doses should be *reduced* in

- **The elderly**
- **Hypotensive patients**
- **Volume contracted patients.**

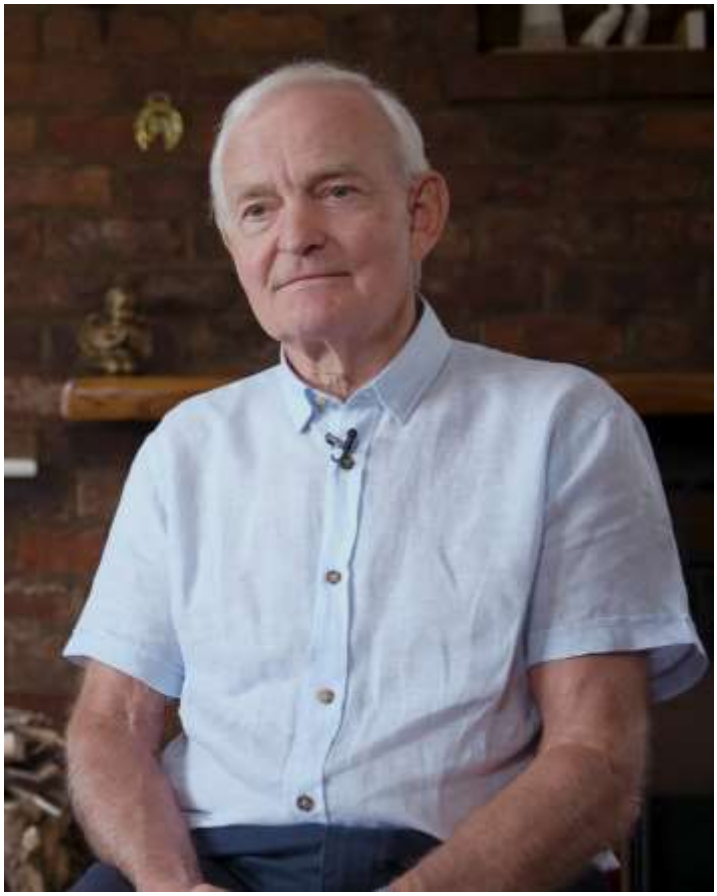
Propofol requirements are also reduced by concomitant administration of opioids and/or benzodiazepines.

Propofol can be given as repeated doses or as a continuous infusion.

Ongoing infusion for **sedation** is titrated to the level of desired effect: **0.3 - 4 mg / kg / hr IV** (for no longer than **48 hours**).

“And the full moon that hangs over, these dreams in the mist....”

“Lovers in a Wood by Moonlight”, oil on canvas, 1873, John Atkinson Grimshaw



John (Iain) Glen, the British Veterinarian who developed propofol, the agent which superseded thiopentone as the world's most commonly used anaesthetic induction agent, (photograph Albert and Mary Lasker Foundation, 2018).

References

1. Propofol in MIMS 1 June 2012.

2. Developing Anaesthesia Textbook v1.6 Dr David Pescod.

3. Australian Medicines Handbook Website, Accessed September 2015.

4. Propofol in RWH Pregnancy & Breastfeeding Guidelines, 20 June 2018.

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