Propofol
Newborn Use Only

2018

Alert	Not advised in haemodynamically unstable neonates. Propofol is not recommended for induction and maintenance of anaesthesia in neonates. There are no data to support the use of propofol infusion for sedation of premature neonates receiving intensive care.
Indication	Premedication for (1) endotracheal intubation and (2) MIST (Minimally Invasive Surfactant Therapy) or InSurE (Intubation, surfactant and extubation) procedure.
Action	The mechanism of action is poorly understood. Propofol is thought to produce its sedative/ anaesthetic effects principally by the positive modulation of the inhibitory function of the neurotransmitter GABA through $GABA_A$ receptors.
Drug Type	General anaesthetic, sedative.
Trade Name	Diprivan, Fresofol 1% injection, Fresofol MCT-LCT 1% emulsion, Propofol – Hospira/Lipuro/Sandoz, Provive 1%, Provive MCT-LCT 1%
Presentation	Ampoule, vial or prefilled syringe 200 mg/20 mL, 500 mg/50 mL or 1 g/100 mL Propofol is a milky-white oil in water emulsion. pH 6 to 8.5. Diprivan contains glycerol, soya oil, egg lecithin, disodium edetate and sodium hydroxide. Propofol Sandoz and Provive 1% contain glycerol, soya oil, egg lecithin and sodium oleate. Fresofol contains glycerol, soya oil, egg lecithin, oleic acid and sodium hydroxide. Fresofol MCT-LCT, Propofol-Lipuro and Provive MCT-LCT contain soya oil, medium chain triglycerides, glycerol, egg lecithin and sodium oleate. Fresofol MCT-LCT contains sodium hydroxide.
Dosage / Interval	**Premedication for endotracheal intubation*** IV: Start at 1 mg/kg and titrate dose of 2.5 mg/kg to infant response (check eye lash reflex every 10 seconds – average ranging from 1.0 to 3.6 mg/kg. **Premedication for MIST or InSurE procedures*** IV 1 mg/kg (maximum 1.5 mg/kg) (CAUTION: Increases the chance of needing non-invasive respiratory support). ***NOTE**: Propofol may be used alone or in combination with other sedatives/analgesics. Reduce propofol dose by 40–60% if combined with other sedatives/analgesics.
Maximum daily dose	Premedication: 6 mg/kg.
Route	IV bolus
Preparation/Dilution	Use undiluted or dilute to a minimum concentration of 2 mg/mL with glucose 5%.
Administration	Slow IV bolus over at least 20 seconds. **Do not use filter**.[20]
Monitoring	Continuous cardiorespiratory monitoring. Resuscitation facilities must be readily available.
Contraindications	Patients allergic to soya, peanut or egg lecithin.
Precautions	Haemodynamically unstable neonates. Neonates with seizures – may be excitatory during recovery phase. With anaesthetic doses, the patient will be apnoeic within 30–90 seconds. Propofol use, especially at increasing doses, is associated with hypotension. Propofol use for MIST and other procedures increased the need for respiratory support and ventilation. Reduce propofol dose by 40–60% for sick patients, or if combined with other sedatives/analgesics.
Drug Interactions	The induction dose requirements of propofol may be reduced in patients with opioids (e.g. morphine, pethidine and fentanyl) and combinations of opioids and sedatives (e.g. benzodiazepines, barbiturates, chloral hydrate and droperidol). Inhalational agents can increase the anaesthetic or sedative and cardiorespiratory effects of propofol.

	Profound hypotension has been reported following anaesthetic induction with propofol in patients treated with rifampicin. A need for lower propofol dose has been observed in patients taking valproate. Propofol does not cause a clinically significant change in onset, intensity or duration of action of the commonly used neuromuscular blocking agents e.g. suxamethonium and non-depolarising muscle relaxants. No significant adverse interactions have been observed with commonly used premedications or drugs used during anaesthesia or sedation (including a range of muscle relaxants, inhalational agents, analgesic agents and local anaesthetic agents). Lower doses of propofol may be required where general anaesthesia is used as an adjunct to regional anaesthetic techniques.
Adverse Reactions	Serious adverse events (including fatalities) have been reported, especially at higher doses. Hypotension and transient apnoea in up to 75% of patients. Arrhythmias, tachycardia. Bradycardia responsive to atropine has been reported. Excitatory phenomena such as involuntary movements, twitches, tremors, hypertonus and hiccup in 14% of patients. Lipaemia and an evolving metabolic acidosis may be precursors of fatal outcomes (propofol infusion syndrome). During the recovery phase, vomiting, headache and shivering in 2% of patients, with nausea occurring more frequently. Tissue necrosis following accidental extravascular administration.
Compatibility	Fluids: Glucose 5%. Y-site: Glucose 5%, sodium chloride 0.9%. Do not mix with other drugs.
Incompatibility	Do not mix with any other fluids or drugs not listed above.
Stability	Do not use if the solution is separated or discoloured.
Storage	Ampoule, vial and syringe: Store below 25°C. Do not freeze. Protect from light.
Special Comments	
Evidence summary	**Efficacy:** **Premedication for intubation**: Durrmeyer et al 2018 [1] in an RCT in 173 neonates undergoing non-emergency, nasotracheal intubation, the frequency of prolonged desaturation did not differ between infants receiving atropine 15 microgram/kg + propofol 2.5 mg/kg [infants >1000 g] or 1 mg/kg [infants <1000g] + additional propofol dose 1 mg/kg if needed, compared to infants receiving atropine 15 microgram/kg + atracurium 0.3 mg/kg + additional 0.1 mg/kg + sufentanil 0.2 microgram/kg [>1000 g] or 0.1 microgram/kg [<1000 g]. The atropine-propofol group had longer mean procedure duration, less frequent excellent quality of sedation, shorter median time to respiratory recovery, shorter time to limb movement recovery (18 versus 60 minutes) and SpO_2 was preserved better in the following hour. van der Lee et al 2016 [2] in n RCT in 22 very preterm newborns undergoing intubation, premedicated with morphine 0.1 mg/kg + vecuronium 0.1 mg/kg versus propofol 2 mg/kg, reported significant hypotension in one infant receiving propofol and no difference in intubating condition score between groups. Penido et al 2011 [3] in an RCT in 20 preterm neonates who underwent tracheal intubation following the use of remifentanil 1 µg/kg + either propofol 2 mg/kg or midazolam 200 µg/kg reported excellent conditions to intubate were observed in 3 neonates that received midazolam and 4 who received propofol, a second attempt to intubate was necessary in 3 patients infused with midazolam and in 2 patients infused with propofol. No differences in pain and stress level before and after the intubation using the NIPS scale and the COMFORT scales. Ghanta et al 2007 [4] reported propofol 2.5 mg/kg (maximum 2 doses) was more effective than morphine 100 microgram/kg atropine, 10 microgram/kg + suxamethonium 2 mg/kg (maximum total dose of 4 mg/kg per intubation attempt) as an induction agent to facilitate neonatal nasotracheal intubation. Time to intubation and recovery time was shorter, hypoxaemia less severe and nasal trauma reduced.

Simons et al 2013 [5] in a case series of 62 intubations in neonates 24 to 44 weeks and 520 to 4380 g assessed premedication with propofol 2 mg/kg starting dose. This was sufficient in 37%. Additional propofol was needed less often on the first postnatal day. The mean dose was 3.3 (SD 1.2) mg/kg. Hypotension occurred in 39%. In 15% of procedures, propofol monotherapy was insufficient.
Conclusion: Propofol with or without the addition of an opioid reduces infant stress and pain and results in improved intubation conditions and relatively short time to recovery. Its use is associated with apnoea, need for assisted ventilation and hypotension. It is not clear if its safety profile warrants its use in newborn infants. (LOR II GOR D)

Premedication for minimally invasive surfactant (MIST) or INSURE procedures: Dekker et al 2018 [6] in an RCT in 78 infants 26 to 36 weeks gestational age receiving MIST procedure reported low-dose sedation with propofol 1 mg/kg increased comfort during MIST procedure in preterm infants, but the need for transient non-invasive ventilation was increased (93% vs 47%). There were no differences in incidence of hypotension (9/30 (30%) vs 2/17 (12%)), bradycardia, intubation or pneumothoraxes. (LOE II)
Dekker et al 2016 [7] in an observational study of very preterm infants receiving MIST, 23 received propofol 1 mg/kg and 15 were not sedated. Preterm infants receiving MIST were more comfortable when sedation was given, but needed ventilation more often (100% versus 33%).
Descamps et al 2017 [8]reported a case series of 35 very preterm infants receiving MIST premedicated with atropine 10 microgram/kg + propofol titration started at 0.5 mg/kg with a mean total dose of 1.5 mg/kg (8 infants also received nalbuphine 0.1 mg/kg).
Conclusion: Low-dose propofol 1 mg/kg before the MIST procedure in preterm infants increased comfort but also the need for transient non-invasive ventilation.(LOE II GOR D)

Analgesia/sedation for procedures including laser for ROP: A single RCT reports the use of protocol + ketamine compared to inhalational anaesthetic for unventilated infants undergoing laser for ROP. Ulgey et al 2015 [9] compared sedation (n = 30) with ketamine 1 mg/kg + propofol 1 mg/kg as a bolus for induction, then propofol 100–150 microgram/kg/min + ketamine 0.25 mg/kg/h for maintenance, versus general anaesthetic (n = 30) induced using 8% sevoflurane with nitrous oxide 50% in oxygen, then maintained with sevoflurane 2% + nitrous oxide 50% in oxygen. Two patients in the sedation group and 11 patients in inhalational anaesthetic group required postoperative mechanical ventilation. Blood pressures and heart rates were similar.
Conclusion: There is insufficient safety and efficacy data for use of propofol infusions as analgesia/sedation in newborns.(LOE II, GOR D)

Pharmacokinetics:
Propofol (2,6-diisopropylphenol) is a highly lipophilic anaesthetic that is metabolised in the liver. Subsequently, its metabolites are eliminated by the renal route. Its clearance mainly depends upon the hepatic blood flow with subsequent glucuronidation or hydroxylation in adults. Propofol disposition is best described by a 3-compartment model, with a rapidly equilibrating central compartment, a second larger peripheral compartment and a third, very large peripheral compartment. Children demonstrate increased clearance and larger volumes of distribution relative to adults, consequently require higher induction and maintenance doses.[10] However, markedly reduced clearance has been reported in neonates.[11, 12] Allegaert et al 2007 [12] reported pharmacokinetics in preterm and neonates after IV bolus administration of propofol 3 mg/kg over 10 seconds. Propofol clearance at 38 weeks PMA was 0.029 L/min. Postmenstrual age (PMA) and postnatal age (PNA) contribute to the inter-individual variability of propofol clearance with very fast maturation of clearance in neonatal life. The addition of a fixed value in neonates with a PNA of ≥10 days resulted in the equation for CL = CL(std).(PMA/38)(11.5) + 0.03] for neonates ≥10 days. Extensive inter-individual variability in propofol clearance (range: 3.7–78.2 ml/kg/min) within the neonatal population has also been reported.[13] Propofol clearance was reduced (typically by 26%) in children who had undergone cardiac surgery.[14]

	Pharmacodynamics: Smits et al 2016 [15] in a dose-finding study in 50 neonates undergoing (semi-)the INSURE procedure reported the propofol ED50 (i.e. effective dose for 50% of patients) for successful intubation for preterm neonates <10 days of age varied between 0.713 and 1.350 mg/kg. Clinical recovery was not attained at the end of the 21-minute scoring period. Mean arterial blood pressure showed a median decrease between 28.5% and 39.1% from baseline with a brief decrease in peripheral and regional cerebral oxygen saturation. **Summary:** 67% of propofol clearance variability in neonates can be explained by PMA and PNA with very fast maturation of clearance in neonatal life. Propofol doses should be reduced in early (PNA of <10 days) life. Preterm neonates and neonates in the first week of postnatal life are at an increased risk for accumulation during either intermittent bolus or continuous administration of propofol. **Safety:** Low dose propofol bolus 1 mg/kg results in moderate reductions in blood pressure with a brief decrease in peripheral and regional cerebral oxygen saturation.[15] Higher doses (mean 3.3 mg/kg) were associated with hypotension in 39% of infants undergoing endotracheal intubation.[5] In infants and children undergoing procedures in Paediatric Critical Care Units, transient respiratory depression and hypotension were associated with propofol delivered by continuous infusion after a loading bolus dose.[16] Propofol infusion syndrome (PRIS) is a sudden onset of treatment-resistant bradycardia leading to asystole, combined with at least one of the following symptoms: lipaemic plasma, clinically enlarged or fat infiltrated liver, metabolic acidosis or rhabdomyolysis. The syndrome was associated with long-duration >48 hours, high-dose >4 mg/kg/h propofol infusions in children under 12 years.[10, 17] In animals, all currently available anaesthetics and sedatives that have been studied, such as ketamine, midazolam, diazepam, clonazepam, propofol, pentobarbital, chloral hydrate, halothane, isoflurane, sevoflurane, enflurane, nitrous oxide and xenon, have been demonstrated to trigger widespread neurodegeneration in the immature brain.[18] No clinical trials of propofol analgesia/sedation report the neurodevelopmental outcome of newborns. In adults, compared with sevoflurane-based general anaesthesia, propofol-based general anaesthesia might decrease the incidence of delayed neurocognitive recovery in older adults after major cancer surgery.[19]
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