Alprostadil (Prostaglandin E_1) 2024

Newborn use only

Alert	1 microgram = 1000 nanograms. Always consult with paediatric cardiologist prior to commencing alprostadil. Prostin VR preparation contains ethanol.
Indication	1. Temporary maintenance of ductus arteriosus patency in duct -dependent congenital heart disease (CHD). 2. Add on medication for unresponsive pulmonary hypertension in congenital diaphragmatic hernia (CDH).
Action	Relaxes the ductus arteriosus in early postnatal life and supports its patency.
Drug Type	Prostaglandin E_1 or PGE_1
Trade Name	Prostin VR.
Presentation	Ampoules (sterile solution) 500 microgram/mL, 1 mL
Dose	**Always consult with paediatric cardiologist prior to commencing alprostadil.** **Starting Dose** **10 nanogram/kg/minute** (range: 5 to 50 nanogram/kg/minute).[1-5] A higher starting dose >10 nanogram/kg/minute is required in hypoxic and haemodynamically unstable infants with CHD.[5,6] Measures are required for the management of apnoea and hypotension at higher doses. **Maintenance Dose** 3-20 nanogram/kg/minute. Aim to administer the lowest dose that safely maintains ductal patency.[1-4] Dose can be increased to a maximum dose of 50 nanogram/kg/minute if there is no clinical or echocardiographic response. Very rarely paediatric cardiologist may suggest a short trial of up to 100 nanogram/kg/minute.
Dose adjustment	Therapeutic hypothermia: No information. ECMO: Higher doses may be required. Renal impairment: No dose adjustment. Hepatic impairment: No dose adjustment.
Maximum dose	Higher doses ≥ 50 nanogram/kg/minute may be needed to resuscitate infants with poor perfusion and oxygenation ('grey baby') and with ductal closure in suspected duct-dependent CHD.
Route	IV
Preparation	**Standard concentration** **Infusion strength** | **Prescribed amount** 1 mL/hour = 10 nanogram/kg/minute | 30 microgram/kg alprostadil and make up to 50 mL **First dilution**: Draw up 1 mL (500 microgram) of alprostadil and add 9 mL of sodium chloride 0.9% to make a final volume of 10 mL with a concentration of 50 microgram/mL.* **Further dilute:** From this, draw up 0.6 mL/kg (30 microgram/kg) and dilute to make a final volume of 50 mL with sodium chloride 0.9% or glucose 5%. Infusing at a rate of **1 mL/hour = 10 nanogram/kg/minute.** *In circumstances where high doses are being used and the 50mL syringe may run out in < 24 hours, up to 3 syringes can be prepared as above at once and connected using a 3-way tap enabling syringes be used in sequence to cover 24 hour period. **HIGH concentration prepared in a 50 mL volume** **Infusion strength** | **Prescribed amount** 1 mL/hour = 50 nanogram/kg/minute | 150 microgram/kg alprostadil and make up to 50 mL **First dilution:** Draw up 1 mL (500 microgram of alprostadil) and add 9 mL of sodium chloride 0.9% to make a final volume of 10 mL with a concentration of 50 microgram/mL. **Further dilute:** **50 mL volume:** draw up 3 mL/kg (150 microgram/kg) of the above solution and dilute to 50 mL with sodium chloride 0.9% or glucose 5%. Infusing at a rate of **1 mL/hour = 50 nanogram/kg/minute.**

	HIGH concentration prepared in a 30 mL volume **Infusion strength** | **Prescribed amount** 1 mL/hour = 50 nanogram/kg/minute | 90 microgram/kg alprostadil and make up to 30 mL **First dilution:** Draw up 1 mL (500 microgram of alprostadil) and add 9 mL of sodium chloride 0.9% to make a final volume of 10 mL with a concentration of 50 microgram/mL. **Further dilute:** **30 mL volume:** draw up 1.8 mL/kg (90 microgram/kg) of the above solution and dilute to make a final volume of 30 mL with sodium chloride 0.9% or glucose 5%. Infusing at a rate of **1 mL/hour = 50 nanogram/kg/minute.**
Administration	Ensure administration is via a vein that has a good blood flow. This can be achieved by peripheral cannula if the limb is adequately perfused or via UVC.[24]
Monitoring	Continuous pulse oximetry, heart rate, ECG and blood pressure monitoring. Assess urine output and peripheral perfusion frequently.
Contraindications	Cyanotic neonates with persistent foetal circulation.[23] Neonates with total anomalous pulmonary venous return below the diaphragm.[23] Neonates with polysplenia or asplenia in whom pulmonary atresia is combined with anomalous pulmonary venous return which may be obstructed.[23]
Precautions	Ensure adequate cardiorespiratory monitoring and cardiorespiratory resuscitation equipment available for immediate use if necessary. Apnoea is frequent. Commencement of alprostadil ≤ 20 nanogram/kg/minute and low maintenance dose reduces apnoea incidence. Titrate to infant's response (increased oxygenation, echo findings and side effects) - Aim is to be on the lowest dose that safely maintains the ductal patency. Hyperosmolar – infuse at concentrations < 20 microgram/mL. Neonates with total anomalous pulmonary venous return below the diaphragm – may precipitate pulmonary oedema because of increased pulmonary blood flow.
Drug Interactions	Concomitant administration with heparin may result in an increased risk of bleeding.
Adverse Reactions	Apnoea is frequent. Commencement of alprostadil ≤ 20 nanogram/kg/minute and low maintenance dose reduces apnoea incidence. Methylxanthines (caffeine or aminophylline) may be used to prevent or treat apnoea.[7, 8] May lower blood pressure by relaxing the vascular smooth muscle causing vasodilatation and can elevate body temperature. Abdominal distension, bradycardia, enterocolitis, vomiting and skin rash.[4,9] Skeletal changes and hypertrophic pyloric stenosis have been reported.[10,11,12] Extravasation may cause tissue necrosis. Flushing – higher incidence with intra-arterial compared with intravenous administration
Overdose	No antidote is available, treatment is symptomatic and supportive. Support respiratory and cardiac function. Monitor pulmonary function, vital signs, ECG and pulse oximetry, and fluid and electrolyte status in patients with significant diarrhoea.[23] Contact the Poisons Information Centre on 13 11 26 (Australia) for information on the management of overdose.
Compatibility	Fluids: Glucose 5%, glucose 10%,[25] sodium chloride 0.9%. Y-site: Adrenaline, Amiodarone, Amino acid solutions, ampicillin, caffeine citrate, calcium gluconate, cefazolin, cefotaxime, chlorothiazide, dobutamine, dopamine, epinephrine, fentanyl citrate, flecainide acetate, furosemide (frusemide), gentamicin sulfate, heparin sodium, methylprednisolone sodium succinate, midazolam hydrochloride, milrinone lactate (only at milrinone concentrations of 0.5 mg/mL in glucose 5%), morphine hydrochloride, pantoprazole sodium, pentoxifylline, potassium chloride, sodium nitroprusside, tobramycin sulfate, vancomycin hydrochloride, vecuronium bromide.

	Uncertain compatibility: Dexmedetomidine, noradrenaline hydrochloride, norepinephrine hydrochloride, SMOFlipid (Alprostadil 20 mcg/mL in D5W approaches the incompatibility threshold with SMOFlipid)
Incompatibility	Fluids: No information Y-site: insulin human regular, levofloxacin, milrinone lactate at concentrations 200 microgram/mL.
Stability	Diluted solution: Stable for up to 24 hours.
Storage	Ampoule: Store at 2 to 8°C. Do not freeze.
Excipients	Ethanol
Special Comments	Do not use if cloudy (crystallised) or hazy. Undiluted solution (500 microgram/mL) is hyperosmolar. Dilute before administration to a concentration of 20 microgram/mL or less.
Evidence	**Background** The incidence of critical congenital heart disease (CCHD) is estimated to be approximately 1.7 in 1000 live births.[2] Maintaining duct patency to optimise the balance of pulmonary and systemic blood flow is the cornerstone strategy in the stabilisation and early clinical care of infants with CCHD. Due to its ability to stimulate endothelium and keep ductus arteriosus open, alprostadil is used in the management of infants awaiting definitive surgical intervention of the CCHD. **Efficacy** **Ductal-dependent congenital heart defects** There are no randomised controlled trials. Cohort studies report a low starting dose of 10 nanogram/kg/min highly effective in hemodynamically stable infants with an antenatally known duct dependent congenital heart disease when started early and before constriction of the ductus arteriosus. A higher starting dose may be required in infants who have a constricting or closed ductus arteriosus and are hemodynamically unstable and hypoxic.[3-6] Level III-3 studies report maintenance of oxygenation and ductal patency with doses of alprostadil 3 to 20 nanogram/kg/minute.[1-4, 13, 14] Level III-3 studies report lower rates of apnoea with alprostadil ≤ 20 nanogram/kg/minute. [1,13] Use of methylxanthines reduced the incidence of apnoea in newborn infants with ductal-dependent congenital heart disease receiving alprostadil.[7,8] Infants on alprostadil infusions who are intubated for transport have higher rates of complications compared to non-intubated infants.[15] (LOE III-3, GOR C) In infants undergoing balloon atrial septostomy, rapid withdrawal of alprostadil infusion may be associated with hypoxaemia.[16] **Pulmonary hypertension** Alprostadil may have beneficial effects in infants with congenital diaphragmatic hernia (CDH) who have unresponsive severe pulmonary hypertension with restrictive ductus arteriosus and suboptimal right ventricle function. [17-19] In a retrospective study, alprostadil was administered to 18 infants with CDH and acute life-threatening pulmonary hypertension who had impaired cardio-respiratory status despite inhaled nitric oxide with or without prostacyclin and sildenafil. All infants were mechanically ventilated and had a bidirectional of exclusively right to left high maximum blood flow velocity (> 150 cm/sec) through the ductus arteriosus. Alprostadil was infused via a central catheter at an initial rate of 25 ng/kg/min. The infusion rate was titrated up or down based on the ductal blood flow velocity (target: 100 cm/sec). The authors reported reduction in the median FiO_2 from 0.80 to 0.35 to keep the preductal saturation between 88 to 96% within in 6 hours after PGE1 commencement.[17] **Pharmacokinetics** Metabolism of PGE_1 is an oxygen-dependent process, occurring in the pulmonary vascular bed and reduced in patients with pulmonary hypertension.[20] There is an increased volume of distribution in patients on ECMO requiring increased infusion rates to maintain ductal patency.[10] (LOE IV, GOR C) **Safety** Reported complications include apnoea (19%), abdominal distension (16%), bradycardia (13%), enterocolitis (6.5%), hypotension (6.5%), vomiting (5%), fever (1.6%) and skin rash (1.6%)[.9, 14] (LOE III-3) With prolonged use, skeletal changes and hypertrophic pyloric stenosis have been reported.[10-12,21] **Caffeine and apnoea:** In a small, randomised control trial (n=42) aminophylline significantly reduced apnoea and the need for endotracheal intubation in infants receiving alprostadil at low doses (10 to 30 nanogram/kg/min).[7] However, no difference was noted in the incidence of apnoea when caffeine was

	used prophylactically at higher dose of alprostadil (40-50 nanogram/kg/min) in a retrospective study involving 64 infants.[8] In a study from New South Wales, apnoea was more likely to occur in non-ventilated infants when alprostadil infusion rate was ≥15 nanogram/kg/minute compared with <15 nanogram/kg/minute, and many infants were transported safely without the need for mechanical ventilation and methylxanthine.[13]
Practice points	
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Authors Contribution of the current version

Current version	Nilkant Phad, Srinivas Bolisetty
Evidence Review	Nilkant Phad, David Osborn (original version)
Expert review	Kathryn Carmo, Hiroko Asakai, Amber Seigel
Nursing Review	
Pharmacy Review	Stephanie Halena, Rebecca O'Grady
ANMF Group contributors	Bhavesh Mehta, Amber Seigel, Rebecca Barzegar, Michelle Jenkins, Mohammad Irfan Azeem, Thao Tran, Natalia Srnic, Susannah Brew, Martin Kluckow, Kerryn Houghton, Benjamin Emerson-Parker, Bryony Malloy, Renae Gengaroli, Samantha Hassall, Sandy Ung, Karel Allegaert
Final editing	Thao Tran
Electronic version	Thao Tran, Cindy Chen, Ian Callander
Facilitator	Srinivas Bolisetty

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