Pancuronium

Newborn Use Only

2017

<table>
<tr><td>Alert</td><td>High-alert medication: High risk of causing significant patient harm when used in error.
This drug should be administered in the presence of personnel trained in advanced airway management.
Suggest regular cessation of infusion for a few to several hours, possibly every 24 hours (commonly referred to as ‘drug holiday’[7]) to assess the need for continued paralysis and adequacy of sedation or analgesia.
Line should be adequately flushed to avoid unintended paralysis during later use of the line.</td></tr>
<tr><td>Indication</td><td>1. Skeletal muscle relaxation or paralysis in mechanically ventilated infants
2. For elective endotracheal intubation.</td></tr>
<tr><td>Action</td><td>Long acting non-depolarising muscle relaxant that competitively antagonises acetylcholine antagonist at nicotinic acetylcholine receptors at neuromuscular junctions. Also has autonomic anticholinergic effect resulting in increase in heart rate.
Onset of action: 1–2 minutes. Duration of action: 45–60 minutes.</td></tr>
<tr><td>Drug Type</td><td>Long acting non-depolarising neuromuscular blocking agent.</td></tr>
<tr><td>Trade Name</td><td>Pancuronium Bromide Injection BP – Astra Zeneca</td></tr>
<tr><td>Presentation</td><td>Ampoules (Polyamp DuoFit), 4 mg/2 mL.</td></tr>
<tr><td>Dosage/Interval</td><td><u>Muscle relaxation</u>
IV bolus: 0.1 mg/kg followed by
(1) Either IV infusion 0.05 mg/kg/hour (0.025–0.075 mg/kg/hour) OR
(2) Intermittent IV bolus 0.05 mg/kg (0.05–0.1 mg/kg) every 1–2 hours.
Note: IV infusion dose can be increased or decreased by 0.01 mg/kg/hour to a maximum of 0.1 mg/kg/hour.

<u>Intubation</u>
IV bolus: 0.1 mg/kg.</td></tr>
<tr><td>Maximum dose</td><td>IV bolus: 0.1 mg/kilogram/dose.</td></tr>
<tr><td>Route</td><td>IV</td></tr>
<tr><td>Preparation/Dilution</td><td>IV bolus:
Draw up 2 mL (4 mg of pancuronium) and add 6 mL water for injection to make a final volume of 8 mL with a concentration of 0.5 mg/mL

IV infusion:
<table>
<tr><th>Infusion rate</th><th>Prescribed amount</th></tr>
<tr><td>1 mL/hour = 50 microgram/kg/hour</td><td>2.5 mg/kg of pancuronium and make up to 50 mL</td></tr>
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Draw up 1.25 mL/kg (2.5 mg/kg of pancuronium) and add sodium chloride 0.9% to make a final volume of 50 mL. Infusing at a rate of 1 mL/hour = 50 microgram/kg/hour.</td></tr>
<tr><td>Administration</td><td>IV bolus: Administer as a rapid intravenous injection over several seconds.
Line should be adequately flushed to avoid unintended paralysis during later use of the line.</td></tr>
<tr><td>Monitoring</td><td>Continuous cardio-respiratory and pulse oximetry monitoring. Close monitoring of neuromuscular function, sedation and blood pressure (invasive or non-invasive) is essential. Monitoring of fluid balance is essential due to of risk of fluid retention. Monitor hepatic and renal function with prolonged use.</td></tr>
<tr><td>Contraindications</td><td>Known hypersensitivity to pancuronium bromide or to the bromide ion.</td></tr>
<tr><td>Precautions</td><td>Avoid prolonged usage.
Suggest regular cessation of infusion, possibly every 24 hours (commonly referred to as ‘drug holiday’) to assess the need for continued paralysis and adequacy of sedation or analgesia.
Pre-existing tachycardia, hypertension (including that associated with renal failure or phaeochromocytoma)—consider an alternative agent.

Renal: Prolonged neuromuscular blockade may occur in renal impairment; reduction in</td></tr>
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	maintenance dose may be necessary. **Hepatic:** Increased onset time and prolonged duration of action may occur in impairment; consider using alternative agent. Myasthenia gravis—prolongs paralysis; avoid neuromuscular blocking agents if possible. Neuromuscular diseases (e.g. dystrophia myotonica, history of polio), severe obesity—unpredictable effect; use cautiously and monitor neuromuscular function closely. Neonates are generally more sensitive to non-depolarising neuromuscular blocking agents; duration of action may be prolonged; monitor neuromuscular function closely. Acidosis, dehydration, hypokalaemia, hypermagnesaemia, hypocalcaemia—enhances effects of neuromuscular blocking drugs; where possible correct before administration, reduce dose and monitor neuromuscular blockade. Hypothermia—decreases effect of pancuronium (unlike the rest of the neuromuscular blockers); reduce dose and monitor neuromuscular blockade. Anaphylactic reaction to neuromuscular blocking agents—allergic cross-reactivity has been reported; refer to specialist for skin testing for sensitivity to other neuromuscular blockers.
Drug Interactions	Drugs that potentiate the effect of pancuronium:[14] 1. Anaesthetics: Halothane, ether, enflurane, isoflurane, methoxyflurane, thiopentone, methohexitone, ketamine and fentanyl. 2. Other drugs: neomycin, streptomycin, kanamycin, gentamicin, bacitracin, polymixins, tetracyclines, piperacillin, diazepam, propranolol, thiamine (high dose), intravenous lignocaine (high dose), magnesium sulfate, lithium carbonate, monoamine oxidase inhibitors (MAOIs), quinine, quinidine, protamine, diuretics, phenytoin, alpha-adrenergic blocking agents, beta-adrenergic blocking agents, calcium channel blockers, imidazoles, metronidazole and magnesium salts, magnesium ions and citrate anticoagulated blood 3. Drugs which are associated with a significant risk of hypokalaemia (e.g. amphotericin B, cisplatin, corticosteroids, loop diuretics, thiazide diuretics) 4. Suxamethonium—prior administration can potentiate the effect of pancuronium Drugs that decrease the effect of pancuronium 1. Neostigmine, edrophonium, adrenaline (epinephrine), azathioprine, theophylline (high dose), potassium chloride, sodium chloride and calcium chloride 2. Hydrocortisone and prednisone can decrease the effect of pancuronium Cardiac glycosides—pancuronium increases the risk of developing arrhythmias.
Adverse Reactions	**Respiratory:** May result in prolonged apnoea or respiratory depression. **Cardiovascular:** After administration, approximately 10% of patients may exhibit mild to moderate increases in blood pressure and/or pulse rate. Dysrhythmias may occasionally occur and increased cardiac output is frequently noted. **Hypersensitivity:** Hypersensitivity reactions occur rarely (< 1%). Bradycardia, bronchospasm, hypotension and cardiovascular collapse have been reported. An occasional transient rash has been reported. Pruritus can occur, as well as rare cases of flushing, oedema and wheezing. **Skin:** A few case reports of local reactions including pain and burning at the site of injection. **Ocular:** Pancuronium decreases intraocular pressure and induces miosis. **Neuromuscular:** Prolonged paralysis, disuse atrophy and areflexia have been reported with prolonged use of pancuronium. **Other:** Hypersalivation may occur, especially if no anticholinergic premedication is given.
Compatibility	Fluids: Glucose 5%, glucose 5% in sodium chloride 0.9%, glucose 5% in sodium chloride 0.45%, Hartmann's, sodium chloride 0.9%.[10] Compatible via Y-site : Adrenaline (epinephrine), aminophylline, cefazolin, dobutamine, dopamine, esmolol, fentanyl, fluconazole, gentamicin, glyceryl trinitrate, heparin, hydrocortisone sodium succinate, lorazepam, midazolam, milrinone, morphine, ranitidine, sodium nitroprusside, trimethoprim-sulfamethoxazole, vancomycin.[10] Compatible in syringe : Heparin (for 5 minutes).[10]

Incompatibility	Incompatible fluids : No information Incompatible via Y site : Barbiturates, caspofungin, furosemide, quinine, thiopentone.[10]
Stability	Dilutions are stable for 48 hours.[9] The stability of pancuronium bromide can be extended if refrigerated. Pancuronium stored at room temperature (15–30°C) will maintain its full clinical potency for 6 months. However, if refrigerated (2–8°C), pancuronium bromide will be stable for up to 3 years or until its expiration date, whichever comes first.
Storage	Store at 2–8°C. Do not freeze. Refrigeration is unnecessary during normal periods of use in operating theatres.
Special Comments	Dose should be individualised for each patient as there is wide variation in individual response. Inhalation agents or prior administration of suxamethonium enhance the intensity of action of pancuronium. Therapeutic: It is recommended that a peripheral nerve stimulator be used to monitor response to pancuronium to minimise the risk of overdose.
Evidence summary	**Efficacy** <u>Muscle relaxation</u> The routine use of pancuronium or any other neuromuscular blocking agent in ventilated newborn infants cannot be recommended. However, for ventilated preterm infants with evidence of asynchronous respiratory effort, neuromuscular paralysis with pancuronium seems to have a favourable effect on intraventricular haemorrhage [RR (95% CI) 0.55 (0.34, 0.89)] and possibly on pneumothorax. However, uncertainty remains regarding the long-term pulmonary and neurological effects and the safety of prolonged use of pancuronium in ventilated newborn infants.[2] (LOEI, GOR B) <u>Intubation</u> Thirty infants with birth weights from 580 to 3450 g (25 to 40 weeks gestation) were prospectively studied during nasotracheal intubation. The infants were randomised to receive atropine 0.01 mg/kg, atropine 0.01 mg/kg plus pancuronium 0.1 mg/kg or no medication (controls) prior to intubation. Pancuronium plus atropine was associated with lesser increases in intracranial pressure and with the least changes in heart rate in response to intubation.[1] (LOEII, GOR C) The dose used in RCTs for neonatal neuromuscular block in mechanically ventilated neonates is 0.03 mg/kg to 0.1 mg/kg.[2] There is one study reporting on use of pancuronium infusion for muscle relaxation in ventilated newborn infants with dose range 0.03–0.07 mg/kg/hour.[8] (LOE IV GOR C) Drug holidays (i.e. stopping neuromuscular blocking agents until forced to restart based on the patient's condition) may decrease the incidence of post-paralytic quadriparesis.[7,18] (LOE IV GOR D) **Pharmacokinetics** Pancuronium's duration of action is approximately 45 to 60 minutes.[11] An average duration of action is 42 minutes following mean doses of intravenous pancuronium of 2.7 mg.[11] Following a single 0.05 mg/kg intravenous pancuronium dose, the 50% recovery time was 37 minutes.[11]. Peak onset of action is at 2–3 minutes.[12] Divided doses of pancuronium may be advantageous in providing rapid, intense paralysis.[13] Pancuronium has been associated with haemodynamic effects (e.g. tachycardia, hypertension) due to blockade of cholinergic receptors outside the neuromuscular junction.[6] Recovery time after paralysis with continuous infusion is faster than that after intermittent bolus injection.[7] A prospective, open-label study conducted in 25 children receiving continuous infusions of pancuronium in ICU showed increased infusion requirement for patients requiring > 5 days

	treatment or for those receiving concomitant anticonvulsant therapy.[8] **Safety** Prolonged administration of pancuronium during the neonatal period is associated with sensorineural hearing loss in childhood survivors of CDH.[4] Pancuronium has been associated with prolonged paralysis and muscle atrophy after 1 week when given as intermittent doses or by continuous infusion.[5] In premature infants, pancuronium has also been associated with joint contractures, specifically in the hips and knees.[6] However, this effect does not appear to persist after discontinuation of the drug and resumption of spontaneous activity.[6] Newborn infants paralysed with pancuronium, despite fluid restriction, had evidence of fluid retention and were significantly heavier that the control infants from day 3 onwards and above their birth weight by day 7. Strict attention to fluid retention is essential when newborns are treated with pancuronium.[17] (LOE III GOR C)
References	1. Kelly MA & Finer NN: Nasotracheal intubation in the neonate: physiologic responses and effects of atropine and pancuronium. J Pediatr 1984; 105:303-309. 2. Cools F, Offringa M. Neuromuscular paralysis for newborn infants receiving mechanical ventilation. Cochrane Database of Systematic Reviews 2005, Issue 2. Art. No.: CD002773. DOI: 10.1002/14651858.CD002773.pub2. 3. Burger,R. Paralysis of ventilated newborn babies does not influence resistance of the total respiratory system. European Respiratory Journal. 14(2):357-62, 1999 Aug. 4. Cheung PY, Tyebkhan JM, Peliowski A, Ainsworth W, Robertson CM. Prolonged use of pancuronium bromide and sensorineural hearing loss in childhood survivors of congenital diaphragmatic hernia. Journal of Pediatrics. 135(2 Pt 1):233-9, 1999 Aug. 5. Rossiter A, Souney PF, McGowan S, Carvajal P. Pancuronium induced prolonged neuromuscular blockade. Crit Care Med 1991;19:1583–7. 6. Fanconi S, Ensner S, Knecht B. Effects of paralysis with pancuronium bromide on joint mobility in premature infants. J Pediatr 1995;127:134–6. 7. Johnson PN, Miller J, Gormley AK. Continuous-Infusion Neuromuscular Blocking Agents in Critically Ill Neonates and Children. Pharmacotherapy 31 (6): 609-620 2011 8. Tobias JD, Lynch A, McDuffee A, Garrett JS. Pancuronium infusion for neuromuscular block in children in the pediatric intensive care unit. Anesth Analg 1995;81:13–16. 9. de Lemos JM, Carr RR, Shalansky KF, Bevan DR, Ronco JJ. Paralysis in the critically ill: intermittent bolus pancuronium compared with continuous infusion. Critical Care Medicine 1999. 27(12):2648-55.. 10. Product Information. AusDI [Internet]. Sydney: Phoenix Medical Publishing; 2006. Updated 23/09/13. 11. Australian Injectable Drugs Handbook. Accessed on 14th December 2016. 12. Ramsey FM: Basic pharmacology of neuromuscular blocking agents. Anesth Clin North Am 1993; 11(2):219-235. 13. AMA Department of Drugs: AMA Drug Evaluations, 5th. American Medical Association, Chicago, IL, 1983. 14. Doherty WG, Breen PJ, Donati F, et al: Accelerated onset of pancuronium with divided doses. Can Anaesth Soc J 1985; 32:1-4. 15. Micomedex solutions. Accessed on 14th December 2016. 16. Berthier JC, Bourgeois J, Sann L, Frappaz D, Damon G, Cochat P, Bethenod M. [Prolonged curarization in the newborn infant under assisted ventilation for idiopathic respiratory distress]. Arch Fr Pediatr. 1983;40:79-83. 17. Greenough A, Gamsu HR, Greenall F. Investigation of the effects of paralysis by pancuronium on heart rate variability, blood pressure and fluid balance. Acta paediatrica Scandinavica. Nov 1989;78(6):829-834 18. Murray MJ, Cowen J, DeBlock H, et al. Clinical practice guidelines for sustained neuromuscular blockade in the adult critically ill patient. Critical care medicine. Jan 2002;30(1):142-156.

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