Argipressin (Vasopressin) 2017
Newborn Use Only

Alert	When using for diabetes insipidus (DI), Paediatric Endocrine consultation should be obtained. Management should be in intensive care where monitoring and expertise are readily available.
Indication	1. Treatment of refractory hypotension. 2. Adjunctive treatment of pulmonary hypertension. 3. Acute antidiuretic hormone (ADH) replacement when diagnosis of diabetes insipidus established. [The drug of choice for the treatment of diabetes insipidus is desmopressin (dDAVP). An argipressin infusion should be considered in the initial management of post-surgical or post-traumatic DI.] 4. Adjunct in acute massive haemorrhage of gastrointestinal tract or oesophageal varices (specialist use only) [Terlipressin or octreotide preferred].
Action	Antidiuretic hormone, also known as arginine vasopressin or argipressin, is a nine amino acid peptide secreted by the posterior pituitary. Its release is mediated either by high serum osmolality or by a hypotension/low right atrial pressure baroreflex. Argipressin acts via V_{1A} receptors in blood vessels, causing vasoconstriction, and via V_2 receptors in the renal tubules, causing anti-diuresis. Argipressin provokes vasodilatation in some vascular beds via its action on oxytocin receptors.
Drug Type	Vasopressor.
Trade Name	Pitressin.
Presentation	Ampoule contains 20 units/1 mL
Dosage / Interval	**For hypotension:** 0.01 to 0.05 units/kg/hour infusion **For pulmonary hypertension:** 0.01 to 0.02 units/kg/hour (can be commenced at 0.006 units/kg/hour to a maximum 0.07 units/kg/hour) **For diabetes insipidus:** Starting dose: 0.5 milliunits/kg/hour Dose range: 0.5 to 1.0 milliunits/kg/hour. May increase to 2.0 milliunits/kg/hour. The final wean may be from 0.5 to 0.25 milliunits/kg/hour **For acute massive gastrointestinal bleeding:** May not be best agent for this indication. Commence argipressin 0.12 units/kg/hour. Increase (titrate) over 2 hours to maximal dose of 0.6 units/kg/hour. Monitor carefully for side effects including fluid retention, electrolyte abnormalities, hypertension and cardiac arrhythmias. If bleeding not controlled at dose < 0.6 units/kg/hour (0.01 units/kg/minute) then unlikely to be controlled at higher doses and other measures should be used.
Maximum daily dose	For hypotension: 0.12 units/kg/hour (0.002 units/kg/minute). [Note up to 0.48 units/kg/hour (0.008 units/kg/minute) has been reported.] For acute massive gastrointestinal bleeding: 0.6 units/kg/hour (0.01 units/kg/min).
Route	Continuous IV infusion.
Preparation/Dilution	**FOR HYPOTENSION/PULMONARY HYPERTENSION:** **Single strength continuous IV infusion**

Infusion strength	**Prescribed amount**
1 mL/hour = 0.05 units/kg/hour	2.5 units/kg argipressin and make up to 50 mL

Draw up 0.125 mL/kg argipressin (2.5 units/kg) and dilute in 50 mL sodium chloride 0.9% or glucose 5% = 0.05 units/kg/mL solution.
Infusing at a rate of **1 mL/hour = 0.05 units/kg/hour.**

DOUBLE STRENGTH continuous IV infusion

Infusion strength	**Prescribed amount**
1 mL/hour = 0.1 units/kg/hour	5 units/kg argipressin and make up to 50 mL

	Dilution: draw up 0.25 mL/kg argipressin (5 units/kg) and dilute in 50 mL sodium chloride 0.9% or glucose 5% = 0.1 units/kg/mL solution. Infusing at a rate of **1 mL/hour = 0.1 units/kg/hour.** **QUADRUPLE STRENGTH continuous IV infusion** **Infusion strength** | **Prescribed amount** **1 mL/hour = 0.2 units/kg/hour** | 10 units/kg argipressin and make up to 50 mL Dilution: draw up 0. 5 mL/kg argipressin (10 units/kg) and dilute in 50 mL sodium chloride 0.9% or glucose 5% = 0.2 units/kg/mL solution. Infusing at a rate of **1 mL/hour = 0.2 units/kg/hour.** **FOR DIABETES INSIPIDUS** **Continuous IV infusion** **Infusion strength** | **Prescribed amount** **1 mL/hour = 0.8 milliunits/kg/hour** | 40 milliunits/kg argipressin and make up to 50 mL. Step 1: Add 0.1 mL (2 units) of argipressin (20 unit/mL ampoule) to 500 mL bag of 0.9% sodium chloride to make a 4 milliunit/mL solution (SOLUTION A). Mix it well. Step 2: Draw up 10 mL/kg of SOLUTION A (40 milliunits/kg) and make up to 50 mL with 0.9% sodium chloride to make a 0.8 milliunits/kg/mL solution. Infusing at a rate of **1 mL/hour = 0.8 milliunits/kg/hour.** **Note: 1 unit = 1000 milliunits.** **FOR GASTROINTESTINAL BLEEDING** **QUADRUPLE STRENGTH continuous IV infusion** **Infusion strength** | **Prescribed amount** **1 mL/hour = 0.2 units/kg/hour** | 10 units/kg argipressin and make up to 50 mL Draw up 0. 5 mL/kg argipressin (10 units/kg) and dilute in 50 mL sodium chloride 0.9% or glucose 5% = 0.2 units/kg/mL solution. Infusing at a rate of **1 mL/hour = 0.2 units/kg/hour.**
Administration	Continuous intravenous infusion via a central line. Use with caution via a peripheral line.
Monitoring	Continuous heart rate, ECG and blood pressure monitoring required. The pressor response should be carefully monitored and may require the weaning of other vasopressors. Assess urine output and peripheral perfusion frequently. Monitor water balance and serum sodium. Observe IV site closely for blanching and extravasation. **For diabetes insipidus:** The dose of this is titrated (usual dose range 0.0005 to 0.001 units/kg/hour (0.5 to 1.0 milliunits/kg/hour), aiming for: • urine output 2–4 mL/kg/hour, • neutral fluid balance, • maintain plasma sodium 145–150 mmol/L Aqueous IV argipressin has a half-life of 20–30 minutes, so a change in infusion rate is reflected 1 hour later.
Contraindications	Hypersensitivity to argipressin.

Precautions	**Use in hypotension:** Argipressin causes water retention and hyponatraemia. May cause ischaemia related to infusion site. Acute ECG or biochemical evidence of myocardial ischaemia. Previously documented chronic and/or severe liver dysfunction (INR > 2, direct bilirubin > 50 micromol/L) or clinical evidence of portal hypertension. Documented or high suspicion of mesenteric ischaemia. **Use in diabetes insipidus:** The mainstay of initial therapy is accurate fluid and electrolyte management. ADH administration should only be considered after a reasonable period of observation establishes that DI is persistent (at least 4–6 hours, but preferably longer in acute situations). Early or over vigorous ADH administration may provoke cerebral oedema, Prior to starting the infusion, it is advisable to allow the patient to drift into a slightly negative fluid balance. This can be easily achieved by not replacing all the previous hour(s) urine output. Once the argipressin infusion has commenced, continue the fluid regimen of replacement of previous hour's losses plus insensible losses. **Use in gastrointestinal bleeding:** There are few reports of argipressin use for gastrointestinal bleeding in newborns. The dose regimen is unclear and other agents may be more effective.
Drug Interactions	Noradrenaline (norepinephrine) and heparin—when used with argipressin may decrease the antidiuretic effect of argipressin.
Adverse Reactions	Causes water retention and hyponatraemia. Early or over vigorous administration may provoke cerebral oedema, Cardiac complications include coronary ischaemia, myocardial infarction, ventricular arrhythmias (ventricular tachycardia and asystole) and severe hypertension. Other reported adverse effects include severe GI ischaemia leading to bowel necrosis, hyponatraemia, anaphylaxis, bronchospasm, urticaria, angioedema, rashes, venous thrombosis, local irritation at injection site and peripheral vasoconstriction leading to cutaneous gangrene.[1,2]
Compatibility	Fluids: Glucose 5%, sodium chloride 0.9% Y-site: Amiodarone, pantoprazole (EDTA-free).
Incompatibility	Fluids: No information. Y-site: Diazepam, furosemide (frusemide), indometacin, phenytoin.
Stability	Diluted solution: Discard remainder after use. Change infusion solution every 24 hours
Storage	Ampoule: Store below 25°C.
Special Comments	Administration via a central line is preferred as extravasation may cause tissue necrosis.
Evidence summary	Efficacy: **Newborns with hypotension:** A pilot trial in preterm infants born < 30 weeks gestation with refractory hypotension (n = 20) of argipressin (0.01 units/kg/h to maximum 0.04 units/kg/hour) versus dopamine (5 to 20 microg/kg/min) reported similar increases in blood pressure. Infants receiving argipressin received fewer doses of surfactant, had lower $PaCO_2$ values and were less tachycardic. No difference in clinical outcome was reported.[3] The role of argipressin for hypotension in newborns is unclear (LOE II, GOR D). **Children with refractory hypotension:** A review[4] of argipressin/terlipressin as rescue therapy in children with catecholamine-resistant shock or cardio-circulatory arrest found 31 reports (428 patients) including a single RCT of argipressin in children with vasodilatory shock. Infants with vasodilatory shock were randomised to low-dose argipressin (0.0005 to 0.002 units/kg/minute = 0.03 to 0.12 units/kg/hour) or placebo in addition to open-label vasoactive agents. There was no difference in time to vasoactive-free haemodynamic stability, a trend to increasing mortality and no benefit in respect to organ-failure-free days from use of argipressin. In observational studies, argipressin from 0.00002 unit/kg/minute to 0.002 unit/kg/minute (0.0012 to 0.12 units/kg/hour) increased blood pressure, urine output, and

decreased serum lactate. In most reports, argipressin and terlipressin led to a reduction of catecholamine dose. However, mortality remained high (188/428; 43.9%) despite the use of argipressin or terlipressin. [4] The role of argipressin for refractory hypotension in newborns is unclear. (LOE IV in newborns, GOR D) American College of Critical Care Medicine Clinical Practice Parameters for Hemodynamic Support of Pediatric and Neonatal Septic Shock included argipressin as an option for management of vasodilatory shock (hypotension with low vascular resistance) refractory to catecholamines including noradrenaline (norepinephrine).[5]

Use in pulmonary hypertension: In a case series of 10 newborn infants with severe persistent pulmonary hypertension of the newborn on nitric oxide, argipressin 0.0002 ± 0.0002 U/kg/minute (0.012 ± 0.012 units/kg/hour) was associated with an improvement in oxygenation index, peak effect 6 hours after initiation, and a reduction in inhaled nitric oxide dose, improvement in blood pressure and urine output ($p < 0.05$), without drop in the serum sodium level or worsening in serum lactate level.[6] The role of argipressin for pulmonary hypertension in newborns is unclear. (LOE IV, GOR D)

Use in congenital diaphragmatic hernia: In a case series of 13 infants with CDH treated with argipressin for refractory hypotension, argipressin (range 0.0001–0.002 units/kg/min) increased mean arterial pressure and decreased pulmonary/systemic pressure ratio, heart rate, and fraction of inspired oxygen. In 6 of 13 patients, extracorporeal membrane oxygenation therapy was no longer indicated after treatment. The role of argipressin in newborns with CDH and refractory hypotension is unclear. (LOE IV, GOR D) [7, 8]

Infants with diabetes insipidus: the drug of choice for the treatment of diabetes insipidus is desmopressin (dDAVP), a synthetic analog of arginine vasopressin, but with a 2,000- to 3,000-fold lower vasopressor effect. An aqueous argipressin infusion should be considered in the initial management of post-surgical or post-traumatic DI. It has the advantage of having a relatively short half-life so that the dose can be titrated against the urine output. It has the disadvantage of requiring significant observation and adjustment of the infusion rate depending upon the hourly urine output. Management should be in PICU where monitoring and expertise are readily available. In children with DI secondary to brain injury, an initial infusion of aqueous argipressin 0.00025 to 0.001 units/kg/hour (0.25 to 1.0 milliunits/kg/hour titrated to urine output 2–3 ml/kg/hour, urine specific gravity 1.010–1.020 and serum sodium 140–145 mEq/L, was effective.[8] Argipressin infusion can be used in infants with diabetes insipidus where dDAVP is not though appropriate. (LOE IV GOR C)

Infants with gastrointestinal bleeding: There are only case reports of argipressin being used for gastrointestinal bleeding.[9,10,11] Argipressin use was reported in 15 children with severe oesophageal variceal bleeding and 2 with peptic ulcer bleeding with control from use of argipressin alone in 9 of 17 episodes. Argipressin was commenced at 0.1 to 0.2 units/minute with titration over 2 hours to control bleeding. The maximum delivered dosage ranged from 0.004 to 0.04 units/kg/min (0.24 to 2.4 units/kg/hour). Control of bleeding did not improve with high dose argipressin and there was a significantly greater incidence of complications in those patients receiving ≥ 0.01 units/kg/min (0.6 units/kg/hour). Complications included electrolyte abnormalities (Na, K, Cl or Ca) in 10 infants, fluid overload (4 infants), hypertension (4 infants) and cardiac dysrhythmias (2 infants).[10]

Meta-analysis of studies in adults with acute variceal bleeds found that although vasopressor agents reduced mortality and achieved haemostasis, trials of argipressin were not conclusive and argipressin was less effective for haemostasis compared to octreotide or somatostatin. [12, 13] Argipressin may be used in combination with nitroglycerin so as to balance its vasoconstrictive effect. Major side effects associated with the use of argipressin include myocardial ischaemia, life threatening arrythmias, mesenteric ischaemia and limb vasoconstriction or ischaemia. Other minor complications include water retention with sodium depletion, benign arrhythmia and acrocyanosis. Monitor cardiac rate and rhythm, and watch for peripheral ischaemia. Terlipressin may be preferred over argipressin as it has the convenience of bolus administration, decreased cardiotoxicity and its ability to control up to 79% of variceal hemorrhage.[14,15] (GOR D)

	Pharmacokinetics: The pharmacology of argipressin in newborns and children has not been sufficiently investigated and data on potential short and long-term adverse effects are still lacking.[14,16] Half-life approximately 30 minutes, clinical duration of action 2–3 hours. **Safety:** Safety data of argipressin in paediatric patients is limited.[14,16] Potent vasoconstrictor action may cause ischaemia. Complications are more common when argipressin is co-administered with moderate to high doses of noradrenaline (norepinephrine). Hyponatraemia occurs frequently during argipressin infusion requiring close monitoring of serum sodium and water intake.[1,2] For control of gastrointestinal haemorrhage, argipressin was associated with electrolyte abnormalities (Na, K, Cl or Ca) in 10 infants, fluid overload (4 infants), hypertension (4 infants) and cardiac dysrhythmias (2 infants), particularly at doses ≥ 0.01 units/kg/minute.[10]
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