Insulin for Hyperkalaemia

Newborn use only

2024

Alert	High risk of hypo and hyperglycaemia necessitating close monitoring of blood sugar levels. **Insulin binds to the plastic of giving sets. Flush the plastic tubing with 20 mL of prepared insulin solution into a receptacle prior to connecting to the infant. This is to saturate the binding.** Insulin concentrations ≤ 0.05 units/mL are not reliably delivered even after preconditioning and flushing.
Indication	Treatment of hyperkalaemia: • Infants with serum potassium (K^+) ≥7.0 mmol/L • Infants with hyperkalaemia and abnormal ECG Management of severe cardiotoxicity or cardiac arrest due to hyperkalaemia
Action	Insulin and glucose activate cellular sodium-potassium ATPase resulting in a potassium shift into the intracellular space.
Drug type	Polypeptide hormone – lowers blood glucose and potassium levels.
Trade name	Actrapid (Novo Nordisk) Humulin R (Eli Lilly)
Presentation	Vial: 100 units/mL in a 10 mL vial. Penfill cartridge: 100 units/mL in 3mL penfill
Dose	**Treatment of hyperkalaemia with insulin—glucose 25% infusion** Starting dose: 0.1 unit/kg/hour. Dose range: 0.05 to 0.2 unit/kg/hour. Titrate infusion rate to serial serum potassium and blood glucose concentrations. **Treatment of hyperkalaemia with insulin-only infusion** Starting dose: 0.1 unit/kg/hour. Dose range: 0.05 to 0.2 unit/kg/hour. Titrate infusion rate to serial serum potassium and blood glucose concentrations. **Must have adequate maintenance fluids to achieve a glucose: insulin ratio of at least 2.5g:1unit to prevent hypoglycaemia.** **Management of severe cardiotoxicity or cardiac arrest due to hyperkalaemia** 0.2 units/kg of insulin in glucose 50% IV over 15 to 30 minutes. **(Use this preparation only if there is insufficient time to prepare insulin—glucose 25% infusion).**
Dose adjustment	Therapeutic hypothermia: Limited data in neonates. ECMO: Limited data in neonates. Renal impairment: Limited data in neonates. Hepatic impairment: Limited data in neonates. Close monitoring of BGL advised due to lability of BGL.
Maximum dose	N/A
Total cumulative dose	N/A
Route	Intravenous
Preparation	**INSULIN—GLUCOSE 25% INFUSION – Run via central line.** Infusion strength: 1 mL/kg/hour = 0.1 unit/kg/hour — Prescribed amount: 5 units insulin and make up to 50 mL Draw up 0.5 mL (50 units of insulin) and add 9.5 mL sodium chloride 0.9%, glucose 5% or glucose 10% to make a final volume of 10 mL with a concentration of 5 units/mL. **FURTHER DILUTE**: Draw up 1 mL (5 units of insulin) of solution and dilute with glucose 25% [25 mL glucose 50% plus 24 mL water for injection] to make a final volume of 50 mL with a concentration/dose rate of **1 mL/kg/hour = 0.1 units/kg/hour.** **INSULIN ONLY INFUSION – Can be infused peripherally.** **Must have adequate maintenance fluids to achieve a glucose: insulin ratio of at least 2.5g:1unit to prevent hypoglycaemia.** Infusion strength: 1 mL/kg/hour = 0.2 unit/kg/hour — Prescribed amount: 10 units insulin and make up to 50 mL

<table>
<tr><td></td><td>Draw up 0.5 mL (50 units of insulin) and add 9.5 mL sodium chloride 0.9%, glucose 5% or glucose 10% to make a final volume of 10 mL with a concentration of 5 units/mL.
FURTHER DILUTE: Draw up 2 mL (10 units of insulin) of solution and dilute with glucose 5%, glucose 10% or sodium chloride 0.9% to make a final volume of 50 mL with a concentration/dose rate of **1 mL/kg/hour = 0.2 units/kg/hour.**

<u>**Cardiac arrest due to hyperkalaemia**</u>
<table><tr><th>Infusion strength</th><th>Prescribed amount</th></tr><tr><td>1 mL/kg/hour = 0.2 units/kg/hour</td><td>10 units insulin and make up to 50 mL</td></tr></table>
Draw up 0.1mL (10 units of insulin) and make up to 50mL with glucose 50% (this contains 25g of glucose). Give 1mL/kg (0.2units/kg of insulin) IV over 15 to 30 minutes. Glucose:insulin ratio = 2.5g:1unit.</td></tr>
<tr><td>**Administration**</td><td>**Intravenous:**
Insulin is adsorbed to the plastic of intravenous bags, syringes and tubing which reduces the delivery of insulin. (1, 2) **To saturate binding to plastic, flush 20 mL of prepared insulin solution through plastic tubing prior to attaching infusion to patient.** Insulin concentrations ≤ 0.05 units/mL are not reliably delivered even after preconditioning and flushing [2].
Infuse with maintenance fluids.
Do not include in maintenance fluid requirements.
Insulin binds to the filter. **Do not filter infusion.**</td></tr>
<tr><td>**Monitoring**</td><td>Blood glucose must be closely monitored to detect either hypo/hyperglycaemia.
Recommend blood glucose every 20 minutes for the first hour, every 30 minutes for the second hour and every 2 to 4 hours thereafter. Increase frequency of monitoring during weaning.
Recommend check potassium within 30–60 minutes of commencing glucose/insulin infusion. Serum potassium should be closely monitored to monitor response to treatment and avoid hypokalaemia.</td></tr>
<tr><td>**Contraindications**</td><td>Hypersensitivity to human insulin or any component of the formulation.
During episodes of hypoglycaemia.</td></tr>
<tr><td>**Precautions**</td><td>Possible adverse effects include hypersensitivity, hypoglycaemia, hyperglycaemia, and hypokalaemia.
Use with caution in cardiac disease, hepatic impairment, renal impairment.</td></tr>
<tr><td>**Drug interactions**</td><td>The following may reduce insulin requirements: Octreotide, beta-adrenergic blocking agents, angiotensin converting enzyme inhibitors, salicylates, anabolic steroids, alpha-adrenergic blocking agents, quinine, quinidine, and sulfonamides.
The following may increase insulin requirements: Thiazides, furosemide, ethacrynic acid, glucocorticoids, thyroid hormones, sympathomimetics, growth hormone, diazoxide.
Sympathomimetics have a potassium lowering effect.</td></tr>
<tr><td>**Adverse reactions**</td><td>Insulin/glucose infusion is associated with a high rate of hyperglycaemia and hypoglycaemia during infusion and hypoglycaemia during weaning (insulin has a longer half-life than glucose).
Hypokalaemia if infusion continued.
Hypertonic solution – potential for extravasation.</td></tr>
<tr><td>**Overdose**</td><td></td></tr>
<tr><td>**Compatibility**</td><td>**Fluids:** Glucose 5%, glucose 10%, glucose 50%, sodium chloride 0.9%
Y-site: Aciclovir, aminophylline, amiodarone (variable), anidulafungin, ascorbic acid, asparaginase, atropine, Azathioprine, aztreonam, benzylpenicillin, bivalirudin, bleomycin, bumetanide, buprenorphine, calcium chloride (variable), calcium gluconate, caspofungin, cefamandole, cefazolin, cefepime, cefotaxime, ceftazidime, ceftaroline, ceftolozane+tazobactam, ceftizoxime, ceftriaxone, cefuroxime, chloramphenicol, clarithromycin, clindamycin, cyanocobalamin, cyclophosphamide, dexamethasone, dexmedetomidine, digoxin (variable), doxapram, enalaprilat, epirubicin, epoetin alfa, erythromycin lactobionate, esmolol, esomeprazole, fentanyl citrate, fluconazole, folic acid (as sodium salt), foscarnet, fosfomycin, fosphenytoin, furosemide (variable), ganciclovir, granisetron, heparin sodium, hydrocortisone, hydromorphone, ibuprofen lysine, imipenem-cilastatin, indomethacin, isovuconazonium sulfate, lidocaine, linezolid, lorazepam, mannitol, magnesium sulfate, meropenem, methadone, methylprednisolone, metoclopramide, metoprolol, metronidazole, mixifloxacin hydrochloride, milrinone, naloxone, nitroglycerin, nitroprusside sodium, octreotide, oxacillin, palonosetron, pamidronate, pancuronium, pantoprazole (variable),</td></tr>
</table>

	paracetamol, pentoxyphylline, phenobarbital, phytomenadione, piperacillin, potassium acetate, potassium chloride; procainamide hydrochloride, promethazine hydrochloride, propofol, pyridoxine, remifentanil, sodium bicarbonate, sodium nitroprusside, streptokinase, sufentanil, tacrolimus, terbutaline, theophylline, thiamine hydrochloride, ticarcillin disodium, ticarcillin disodium-clavulanate potassium, tigecycline, urokinase, vancomycin, vecuronium, verapamil, voriconazole and zoledronic acid **In syringe:** Insulin NPH.
Incompatibility	**Y-site:** Alprostadil, cefoperazone, cefoxitin, chlorpromazine, dantrolene sodium, diazepam, diazoxide, dobutamine, famotidine (variable), gentamicin (variable), glycopyrrolate, hydralazine (variable), isoprenaline, ketamine, labetalol, metaraminol (variable), micafungin, noradrenaline (norepinephrine)(variable), ondansetron (variable), phentolamine, phenylephrine, phenytoin, piperacillin-tazobactam, polymyxin, propranolol, protamine, rocuronium, sulfamethoxazole-trimethoprim, tobramycin, vasopressin (variable)
Stability	Prepared solutions are stable at room temperature (< 25°C) for 24 hours. A 20 mL insulin priming solution at a concentration of 0.1 units per mL was found to deliver 80% of the expected insulin (1). A 20 mL insulin priming solution with additional preconditioning for 1 hour at a concentration of 0.05 units per mL was found to deliver 26.5% of the expected insulin (2).
Storage	Store human insulin preparations between 2 and 8°C. Do not freeze. Human insulin preparations which have been frozen must not be used. Protect from excessive heat and light. Should appear clear and colourless. After first use, the vials may be kept at room temperature (below 25°C) for 28 days.
Excipients	Actrapid: glycerol, metacresol, zinc chloride, water for injection, hydrochloric acid, sodium hydroxide Humulin R: glycerol, hydrochloric acid, metacresol, sodium hydroxide, water for injection
Special comments	Recommend administer insulin/glucose in same line as intravenous fluids. Recommend intravenous fluids and/or an additional glucose 25% syringe placed proximally for rapid treatment of hypoglycaemia if needed. Do not include insulin glucose in the total daily fluid intake. Frequent blood glucose and potassiummeasurements, especially after commencement and during weaning of infusion are needed for titration and safety
Evidence	**Efficacy** **Treatment of hyperkalaemia:** A systematic review (3) of interventions for neonatal hyperkalaemia found 2 studies (4, 5) comparing insulin/glucose infusion versus rectal cation-resin. Meta-analysis of 2 studies (52 infants) found no difference in cardiac arrhythmias (RR 0.29; 95% CI 0.05, 1.65); or all-cause mortality [RR 0.18; 0.03, 1.15]. Malone 1991, using an insulin infusion 0.05 to 0.2 units/kg/hour in albumin 5%, reported reduced treatment failure (rise in K+ concentration > 0.5 mmol/L or K+ > 7 mmol/L) of borderline statistical significance (RR 0.07; 0.00 to 1.01; RD -1.00; -1.28 to -0.72) compared to resin (5). Hu 1999, using a glucose/insulin infusion with glucose 10–15 g:insulin 1 unit, reported a reduction in duration of hyperkalaemia (MD -12.20 hours; -20.95, -3.45); no difference in peak serum K+ (MD -0.10 mmol/L; -0.57, 0.37); a reduction in IVH (RR 0.3; 0.10, 0.93) and IVH grades ≥ 2 (RR 0.3; 0.10, 0.93) compared to resin; and no infant with hypoglycaemia in either group (4). No study compared insulin-glucose with a beta-agonist. Conclusion: The combination of insulin and glucose is preferred over treatment with rectal cation-resin for hyperkalaemia in preterm infants (3). (LOE I GOR C) **Glucose:insulin ratio:** It is recommended to neutralise insulin in the glucose-insulin infusion for hyperkalaemia by using safe glucose:insulin ratio to prevent hypoglycemia. Several ratios ranging from 2.5:1 to 10:1 have been reported in literature (6,7). To balance the risk of hyper or hypoglycemia, a historical control study compared infusions with lower glucose: insulin ratio 3.3g:1 unit (glucose 20%) versus a higher glucose:insulin ratio 5 g:1 unit (glucose 30%) for treatment of hyperkalaemia in neonates. This study reported reduced rates of moderate hyperglycaemia [77% to 21.7% (p = 0.001)] with a single infant in the lower arm having hypoglycaemia (8). (LOE III-3, GOR C).

	Management of severe cardiotoxicity or cardiac arrest due to hyperkalaemia: The Pediatric Advanced Life Support guidelines (9), Advanced Cardiac Life Support guidelines (10) and a simulation trial of medication preparation and delivery (11) support the following sequence of medications to treat hyperkalaemia during paediatric cardiac: First, calcium; second, sodium bicarbonate; and third, insulin with glucose. Recommended dose [adult guideline]: Glucose plus insulin: mix 25 g (50 mL of glucose 50%) glucose and 10 units regular insulin and give IV over 15 to 30 minutes. Glucose:insulin ratio = 2.5 g:1 unit. **Pharmacokinetics** Following IV administration, the observed half-life of insulin ranges from 5 to 15 minutes (12).
Practice points	
References	1. Thompson CD, Vital-Carona J, Faustino EV. The effect of tubing dwell time on insulin adsorption during intravenous insulin infusions. Diabetes Technol Ther. 2012; 14:912-6. 2. Hewson M, Nawadra V, Oliver J, Odgers C, Plummer J, Simmer K. Insulin infusions in the neonatal unit: delivery variation due to adsorption. J Paediatr Child Health. 2000; 36:216-20. 3. Vemgal P, Ohlsson A. Interventions for non-oliguric hyperkalaemia in preterm neonates. Cochrane Database Syst Rev. 2012:CD005257. 4. Hu PS, Su BH, Peng CT, Tsai CH. Glucose, and insulin infusion versus kayexalate for the early treatment of non-oliguric hyperkalemia in very-low-birth-weight infants. Acta Paediatr Taiwan. 1999; 40:314-8. 5. Malone TA. Glucose and insulin versus cation-exchange resin for the treatment of hyperkalemia in very low birth weight infants. J Pediatr. 1991; 118:121-3. 6. Harel Z, Kamel KS. Optimal Dose and Method of Administration of Intravenous Insulin in the Management of Emergency Hyperkalemia: A Systematic Review. PLoS One. 2016 May 5;11(5): e0154963. 7. Humphrey TJL, James G, Wilkinson IB, Hiemstra TF. Clinical outcomes associated with the emergency treatment of hyperkalaemia with intravenous insulin-dextrose. Eur J Intern Med. 2022 Jan; 95:87-92 8. Oschman A, Gansen A, Kilbride H, Sandritter T. Safety, and efficacy of two potassium cocktail formulations for treatment of neonatal hyperkalemia. Ann Pharmacother. 2011; 45:1371-7. 9. American Heart Association. Web-based Integrated Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care – Part 12: Pediatric Advanced Life Support. ECCguidelines.heart.org. 10. American Heart Association. Web-based Integrated Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care – Part 10: Special Circumstances of Resuscitation. ECCguidelines.heart.org. 11. Arnholt AM, Duval-Arnould JM, McNamara LM, et al. Comparatively Evaluating Medication Preparation Sequences for Treatment of Hyperkalemia in Pediatric Cardiac Arrest: A Prospective, Randomized, Simulation-Based Study. Pediatr Crit Care Med. 2015;16: e224-30. 12. MerativeTM Micromedex® Complete IV Compatibility (electronic version). Merative, Ann Arbor, Michigan, USA. Available at: https://www.micromedexsolutions.com/ (cited: June/11/2024).

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