Insulin for Hyperglycaemia

Newborn Use Only

2022

<table>
<tr><td>Alert</td><td>High risk medication in A PINCH Medicines list under New South Wales Clinical Excellence Commission.
Different brands of insulin are not bioequivalent. Do not substitute between brands.[13]
Actrapid is the ANMF group's recommended short-acting insulin for IV infusion in neonates.
International units are hereafter referred to as "units".
High risk of hypoglycaemia.
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 Unit/mL are not reliably delivered even after preconditioning and flushing.</td></tr>
<tr><td>Indication</td><td>Treatment of persistent hyperglycaemia.
[For treatment of hyperkalaemia, see Insulin – hyperkalaemia].</td></tr>
<tr><td>Action</td><td>Insulin is a polypeptide hormone that acts on cells throughout the body to stimulate uptake, utilisation and storage of glucose resulting in a lowering of blood glucose. Insulin stimulates the liver to store glucose in the form of glycogen and facilitates the entry of glucose into muscle and adipose tissue. It inhibits lipolysis, proteolysis and gluconeogenesis, enhances protein synthesis and conversion of excess glucose into fat.</td></tr>
<tr><td>Drug type</td><td>Polypeptide hormone – lowers blood glucose.</td></tr>
<tr><td>Trade name</td><td>Actrapid [Novo Nordisk]</td></tr>
<tr><td>Presentation</td><td>100 units/mL in a 10 mL vial and 3 mL Penfill.</td></tr>
<tr><td>Dose</td><td>Treatment of hyperglycaemia:
<u>Intravenous:</u>
Starting dose: 0.05 unit/kg/hour.
Dose range: 0.01 to 0.1 unit/kg/hour.
Titrate in small increments to blood glucose: Target blood glucose level (BGL) 8 to 10 mmol/L [1, 2].</td></tr>
<tr><td>Dose adjustment</td><td>Therapeutic hypothermia: Limited evidence in neonates. Higher dose may be required to maintain euglycemia [3].
ECMO: Data limited in pre term neonates to make recommendation.
Renal impairment: Limited data in neonates. Lower doses may be required in severe renal failure.
Hepatic impairment: Limited data in neonates. Close monitoring of BGL advised due to lability of BGL [4].</td></tr>
<tr><td>Maximum dose</td><td></td></tr>
<tr><td>Total cumulative dose</td><td></td></tr>
<tr><td>Route</td><td>IV</td></tr>
<tr><td>Preparation</td><td>NOTE: 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.

SINGLE STRENGTH INFUSION (suitable if weight > 1 kg)
<table>
<tr><th>Infusion strength</th><th>Prescribed amount</th></tr>
<tr><td>1 mL/hour = 0.1 unit/kg/hour</td><td>5 unit/kg insulin and make up to 50 mL</td></tr>
</table>
Draw up 0.6 mL (60 units of insulin) and add 29.4 mL glucose 5%, glucose 10% or sodium chloride 0.9% to make a final volume of 30 mL with a concentration of 2 unit/mL.
FURTHER DILUTE: 2.5 mL/kg (5 units/kg) of the above solution and dilute with glucose 5%, glucose 10% or sodium chloride 0.9% to a final volume of 50 mL with a concentration of 0.1 unit/kg in each mL.
Infusion at 1 mL/hour = 0.1 unit/kg/hour

DOUBLE STRENGTH INFUSION
<table>
<tr><th>Infusion strength</th><th>Prescribed amount</th></tr>
<tr><td>1 mL/hour = 0.2 unit/kg/hour</td><td>10 unit/kg insulin and make up to 50 mL</td></tr>
</table>
Draw up 0.6 mL (60 units of insulin) and add 29.4 mL glucose 5%, glucose 10% or sodium chloride 0.9% to make a final volume of 30 mL with a concentration of 2 unit/mL.
FURTHER DILUTE: 5 mL/kg (10 unit/kg) of the above solution and dilute with glucose 5%, glucose 10% or sodium chloride 0.9% to a final volume of 50 mL with a concentration of 0.2 unit/kg in each mL.
Infusion at 1mL/hour = 0.2 unit/kg/hour</td></tr>
<tr><td>Administration</td><td>Intravenous: 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.
Do not filter infusion. Insulin also binds to the filter.
Can be infused with maintenance fluids. Recommend attaching insulin infusion after the filter.</td></tr>
</table>

	Do not bolus other drugs through this line.
Monitoring	Blood glucose level (BGL) After Initiation of infusion: 30 minutes-2 hours based on the infant's risk profile until stabilised. On maintenance: 4–6 hourly. After cessation of infusion: At 1 hour. Alteration of infusion: Within 1 hour. Serum potassium concentration.
Contraindications	Hypersensitivity to regular insulin or any of its components. During episodes of hypoglycaemia.
Precautions	Hypoglycaemia is a common adverse effect. Blood glucose must be monitored closely to detect hypoglycaemia. Do not adjust the rate of the maintenance solution or other infusions when insulin is commenced or the insulin infusion rate is altered. For example, if insulin is commenced or the rate of the insulin infusion is increased, do not turn down the maintenance solution to compensate for the total volume delivered. The amount of glucose being delivered to the infant will then be reduced as the insulin is commenced or dose is increased, possibly causing hypoglycaemia in an already unstable infant. If ceasing insulin or changing the strength, be careful to remove and replace the previous line and T-piece to avoid flushing through insulin remaining in the tubing. Administer IV bolus medication via separate IV access to avoid insulin bolus administration.
Drug interactions	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, octreotide, growth hormone, and diazoxide. Beta blocking agents may mask the symptoms of hypoglycaemia and delay recovery from hypoglycaemia. Hypoglycaemia in the presence of concomitant use of a beta-adrenergic blocking agent may precipitate a hypertensive crisis.
Adverse reactions	Hypoglycaemia; hypokalaemia; and hyponatraemia. Urticaria and anaphylaxis (extremely rare). Insulin resistance may develop resulting in a larger dose requirement.
Compatibility	**Fluids:** glucose 5%, glucose 10%, glucose 50%, sodium chloride 0.9%. **Y-site:**[12,13] Aciclovir, aminophylline, amphoteiricin B lipid complex, atenolol, atropine, azathioprine, aztreonam, calcium chloride, calcium gluconate, caspofungin, cefazolin, cefepime, cefotaxime, ceftazidime, ceftriaxone, cefuroxime, chloramphenicol, clindamycin, cloxacillin, dexamethasone, enalaprilat, epoetin alfa, erythromycin lactobionate, fentanyl, fluconazole, folic acid, fosphenytoin, ganciclovir, hydrocortisone, ibuprofen, imipenem-cilastatin, indomethacin, lidocaine , linezolid, magnesium sulfate, Meropenem, methadone, methylprednisolone, metoclopramide, metoprolol, metronidazole, milrinone, naloxone, nitroglycerin, nitroprusside, octreotide, pamidronate, pancuronium, penicillin G, pentobarbital, pentoxifylline, phenobarbital, potassium acetate, potassium chloride, propofol, pyridoxine, remifentanil, sodium bicarbonate, streptokinase, thiamine, ticarcillin –clavulanate, urokinase, vancomycin, vecuronium, verapamil, vitamin B complex with C. **Variable compatibility:**[12] amikacin, amiodarone, amphotericin B conventional, ampicillin, cyclosporine, digoxin, dobutamine, dopamine, epinephrine, furosemide, gentamicin, heparin, hydralazine, midazolam, morphine sulfate, multiple vitamin injection, norepinephrine, ondansetron, pantoprazole, tobramycin, vasopressin.
Incompatibility	**Y-site administration:**[12,13] Cefoxitin, diazepam, diazoxide, glycopyrrolate, ketamine, labetalol, phenytoin, piperacillin -tazobactam, propranolol, protamine,rocuronium, sulfamethoxazole-trimethoprim
Stability	Actrapid: Prepared solutions are stable at room temperature (< 25°C) for 24 hours. (extrapolated from Insulin Human Regular) [12]
Storage	Store human insulin between 2 and 8°C. Do not freeze. Protect from excessive heat and light. Should appear clear and colourless. While it is suggested that insulin vials can be kept for 28 days after the first use, ANMF consensus recommendation is to avoid this practice because of the risk of microbial contamination and increased susceptibility of neonates to sepsis.

Excipients	Glycerol, metacresol, zinc chloride, water for injections. Hydrochloric acid and sodium hydroxide are used to adjust the pH. Contains less than 1 mmol sodium (23 mg) per dose, i.e. is essentially 'sodium-free'.
Special comments	Insulin is adsorbed to the plastic of intravenous bags, syringes, and tubing which reduces the delivery of insulin [5-7]. Twenty mL of insulin priming solution at concentrations of 0.1 unit/mL and 0.05 unit/mL were found to deliver 80% and 26.5% of the expected insulin. Insulin concentrations ≤ 0.05 unit/mL are not reliably delivered even after preconditioning and flushing [5, 6].
Evidence	**Efficacy** **Treatment of hyperglycaemia in very low birth weight infants:** Systematic review [2] of trials of insulin infusion for treatment of neonatal hyperglycaemia found that use of an insulin infusion obviates the need to decrease the concentration of glucose prescribed and optimised the utilisation of calories by the infant resulting in significant increases in non-protein energy intake, glucose intake and short-term weight gain. However, insulin infusion had no significant effect on death, severe intraventricular haemorrhage, retinopathy of prematurity, bacterial sepsis, fungal sepsis or necrotising enterocolitis; effects on other major morbidities were not assessed. These trials did not report an excess of hypoglycaemia, possibly due to the more liberal target BSLs: Collins 1991 [8] 4.4–9.9 mmol/L and Meetze 1998 [9] 5.5–9.9 mmol/L. Conclusion: Evidence from randomised trials in hyperglycaemic VLBW neonates is insufficient to determine the effects of treatment on death or major morbidities. [2] [LOE I GOR D] **Prevention of neonatal hyperglycaemia in very low birth weight infants:** Systematic review [10] of trials of early insulin infusion for prevention of neonatal hyperglycaemia found that use of an insulin infusion reduced hyperglycaemia but increased death before 28 days and increased the risk of hypoglycaemia. The reduction in hyperglycaemia was not accompanied by significant effects on major morbidities; effects on neurodevelopment are awaited. The evidence does not support the routine use of insulin infusions to prevent hyperglycaemia in VLBW neonates. [10][LOE I GOR B] **Tight glycaemic control with insulin in hyperglycaemic very low birth weight infants:** RCT in infants born at < 30 weeks' gestation or < 1500 g with hyperglycaemia (2 consecutive BGL > 8.5 mmol/L 4 hours apart) randomly assigned to tight glycaemic control with insulin (target BGL 4–6 mmol/L) or restrictive guidelines for starting insulin (target BGL 8–10 mmol/L). Infants in the tight group had a lesser lower leg growth rate ($P < 0.05$), but greater head circumference growth ($P < 0.0005$) and greater weight gain ($P < 0.001$) to 36 weeks' postmenstrual age than control infants. Tight group infants had lower daily BGL and greater incidence of hypoglycaemia (BGL < 2.6 mmol/L) (25/43 vs 12/45; $P < 0.01$) than controls. There were no significant differences in nutritional intake or in the incidences of mortality or morbidity. The balance of risks and benefits of insulin treatment in hyperglycaemic pre-term neonates remains uncertain. [1] [LOE II GOR D] Guidelines: ESPGHAN 2005 recommended the use of insulin should be restricted to conditions where reasonable changes in glucose infusion rate do not control marked hyperglycaemia. [11] Although this recommendation is now out of date, current evidence is consistent with this recommendation. **Pharmacokinetics** Following IV administration, the observed half-life of insulin ranges from 5 to 15 minutes. [12]
Practice points	
References	1. Alsweiler JM, Harding JE, Bloomfield FH. Tight glycemic control with insulin in hyperglycemic preterm babies: a randomized controlled trial. Pediatrics. 2012;129:639-47. 2. Bottino M, Cowett RM, Sinclair JC. Interventions for treatment of neonatal hyperglycemia in very low birth weight infants. Cochrane Database Syst Rev. 2011:CD007453. 3. Cueni-Villoz N, Devigili A, et al. Increased blood glucose variability during therapeutic hypothermia and outcome after cardiac arrest. Crit Care Med. 2011 Oct; 39(10):2225-31. 4. Scheen AJ. Pharmacokinetic and toxicological considerations for the treatment of diabetes in patients with liver disease. Expert Opin Drug Metab Toxicol. 2014; 10:839-857. 5. 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. 6. 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.

	7. Simeon PS, Geffner ME, Levin SR, et al. Continuous insulin infusions in neonates: pharmacologic availability of insulin in intravenous solutions. Journal of Pediatrics. 1994; 124:818-20. 8. Collins JW, Jr., Hoppe M, Brown K, Edidin DV, Padbury J, Ogata ES. A controlled trial of insulin infusion and parenteral nutrition in extremely low birth weight infants with glucose intolerance. J Pediatr. 1991; 118:921-7. 9. Meetze W, Bowsher R, Compton J, Moorehead H. Hyperglycemia in extremely- low-birthweight infants. Biol Neonate. 1998;74:214-21. 10. Sinclair JC, Bottino M, Cowett RM. Interventions for prevention of neonatal hyperglycemia in very low birth weight infants. Cochrane Database Syst Rev. 2011:CD007615. 11. Koletzko B, Goulet O, Hunt J, Krohn K, Shamir. Guidelines on Paediatric Parenteral Nutrition of the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and the European Society for Clinical Nutrition and Metabolism (ESPEN), Supported by the European Society of Paediatric Research (ESPR). J Pediatr Gastroenterol Nutr. 2005; 41 Suppl 2:S1-87. 12. Micromedex. Insulin Human Regular. Accessed on 9 March 2021. 13. Australian Injectable Drugs Handbook, 8th Edition. Accessed on 28 October 2020. https://aidh.hcn.com.au/browse/i/insulin_for_subcutaneous_or_iv_use 14. Human Insulin (rys). Product Information. Accessed on 28 October 2020. 15. Humulin Preparations. Product Information. Accessed on 28 October 2020.

VERSION/NUMBER	DATE
Original	3/05/2017
Revised 1.1 Revised 1.2 Revised 2.0 Revised 3.0	19/05/2017 20/06/2017 18/03/2021 24/06/2022
Current 3.0 (minor errata)	19/06/2025
REVIEW	24/06/2027

Authors Contribution

Original author/s	Srinivas Bolisetty
Evidence Review	David Osborn
Expert review	Charles Verge, Shihab Hameed, Uma Visser
Nursing Review	Ruth Jackson, Celia Cunha Brites, Charles Tian, Tiffany Kwan
Pharmacy Review	Cindy Chen, Rebecca O'Grady, Mohammad Irfan Azeem, Kerrie Knox, Thao Tran, Michelle Jenkins
ANMF Group contributors	Nilkant Phad, Bhavesh Mehta, Amber Seigel, Rebecca Barzegar, Jutta van den Boom, Bryony Malloy, Samantha Hassall, Susanah Brew
Final editing and review of the original	Ian Whyte
Electronic version	Cindy Chen, Thao Tran, Ian Callander
Facilitator	Srinivas Bolisetty