Insulin - Hyperglycaemia

Alert
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.

Indication
Treatment of persistent hyperglycaemia.
[For treatment of hyperkalaemia, see Insulin – hyperkalaemia].

Action
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.

Drug Type
Polypeptide hormone – lowers blood glucose.

Trade Name
Actrapid [Novo Nordisk]
Humulin R [Eli Lilly]
Hypurin Neutral Injection [Aspen]

Presentation
Vial: 100 units/mL in a 10 mL vial

Dosage/Interval
Treatment of hyperglycaemia:

<table>
<thead>
<tr>
<th>Route</th>
<th>SINGLE STRENGTH INFUSION (suitable if weight &gt; 1 kg)</th>
<th>Prescribed amount</th>
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<tbody>
<tr>
<td>IV</td>
<td>Infusion strength</td>
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<tr>
<td></td>
<td>1 mL/hour = 0.1 unit/kg/hour</td>
<td>5 unit/kg insulin and make up to 50 mL</td>
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<td></td>
<td>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.</td>
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<td>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</td>
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<td></td>
<td>Infusion at 1 mL/h = 0.1 unit/kg/hour</td>
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<table>
<thead>
<tr>
<th>Route</th>
<th>DOUBLE STRENGTH INFUSION</th>
<th>Prescribed amount</th>
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<tr>
<td>IV</td>
<td>Infusion strength</td>
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<td></td>
<td>1 mL/hour = 0.2 unit/kg/hour</td>
<td>10 unit/kg insulin and make up to 50 mL</td>
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<td>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.</td>
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<td>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 0.1 unit/kg in each mL</td>
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<td></td>
<td>Infusion at 1 mL/h = 0.2 unit/kg/hour</td>
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</table>

Administration
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.
Do not bolus other drugs through this line.

Monitoring
Blood glucose concentration
Initiation: Every 30 minutes until stabilised.
Stabilisation: 4–6 hourly
After cessation of infusion: At 30 minutes and at 1 hour
Alteration of infusion: Within 1 hour
**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: Thiadizides, furosemide, ethacrynic acid, glucocorticoids, thyroid hormones, sympathomimetics, growth hormone, diazoxide.

**Adverse Reactions**

Hypoglycaemia; hypokalaemia; and hyponatraemia.

**Compatibility**

Fluids: Amino acid solution, glucose 5%, glucose 10%, glucose 50%, lipid emulsion, sodium chloride 0.9%.

Y-site administration: Amiodarone, azathioprine sodium; aztreonam; bretylum tosylate; bumetanide; buprenorphine hydrochloride; calcium chloride dihydrate; calcium gluconate monohydrate; caspofungin acetate; cefazolin sodium; cefepime hydrochloride; cefotaxime; ceftazidime; ceftriaxone sodium; cefuroxime; chloramphenicol sodium succinate; clindamycin phosphate; cyanocobalamin; dexamethasone sodium phosphate; enalaprilat; epirubicin hydrochloride; epoetin alfa; erythromycin lactobionate; fentanyl citrate; fluconazole; folic acid (as sodium salt); fosfomycin sodium; ganciclovir sodium; hydrocortisone sodium succinate; ibuprofen lysine; imipenem-cilastatin sodium; indometacin sodium trihydrate; lactated ringer's injection; lidocaine hydrochloride; magnesium sulfate; mannitol; meropenem; methadone hydrochloride; methylprednisolone sodium succinate; metoclopramide hydrochloride; metoprolol tartrate; metronidazole; milrinone lactate; naloxone hydrochloride; nitroglycerin; nitroprusside sodium; octreotide acetate; pancuronium bromide; penicillin G potassium; penicillin G sodium; phenobarbital sodium; phenylephrine; phenytoin; piperacillin sodium; potassium acetate; potassium chloride; procainamide hydrochloride; promethazine hydrochloride; propofol; pyridoxine hydrochloride; remifentanil hydrochloride; sodium bicarbonate; streptokinase; sufielxat sodium; tacrolimus; terbutaline sulfate; thiamine hydrochloride; ticarcillin disodium; ticarcillin disodium-clavulanate potassium; urokinase; vancomycin hydrochloride; vecuronium bromide; verapamil hydrochloride; voriconazole in syringe: Insulin NPH.

**Incompatibility**

Y-site administration: Cefoxitin; chlorpromazine; diazepam; dixazone; dopamine; glycopyrrolate; isoprenaline; ketamine; labetalol; noradrenaline (norepinephrine); phenolamine; phenylephrine; phentoin; piperacillin sodium-tazobactam sodium; polymyxin; propranolol; protamine; quinidine; vecuronium; sulfamethoxazole-trimethoprim.

**Stability**

Actrapid: Prepared solutions are stable at room temperature (<25°C) for 24 hours.

Humulin R: Prepared infusions can be stored refrigerated for 48 hours and may be used at room temperature for an additional 48 hours.

Novolin R: Prepared solutions are stable for 24 hours at room temperature [Micromedex].

**Storage**

Store human insulin preparations between 2 and 8°C. The shelf life is 30 months when stored 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
Insulin is incompatible with many drugs and hence should be administered via a single, dedicated line. Insulin is adsorbed to the plastic of intravenous bags, syringes, and tubing which reduces the delivery of insulin [3-5]. 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 [3,4].

**Evidence summary**

**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 [6] 4.4–9.9 mmol/L and Meetze 1998 [7] 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 [8] 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. [8]. (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 (BG < 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. (LOE II GOR D) [1].

**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 [9]. 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 [Micromedex].

**References**