

Newborn Use Only

Diazoxide

2016

Alert	Concomitant use of a thiazide diuretic is recommended. Avoid higher doses where possible.
Indication	Treatment of neonatal hyperinsulinaemic hypoglycaemia (transient or persistent).
Action	Opens potassium-ATP channels on pancreatic beta-cells to inhibit insulin secretion. Opening of these channels also occurs in cardiac and vascular smooth muscle leading to decrease in blood pressure and potential for cardiorespiratory deterioration.
Drug Type	Antihypertensive, antidiuretic benzothiadiazine.
Trade Name	Oral: Proglycem. Intravenous: DBL Diazoxide Injection BP.
Presentation	Oral: Diazoxide 10 mg/mL solution compounded in house by the Pharmacy department; 50 mg/mL commercial oral preparation available as an unregistered product. Intravenous: DBL Diazoxide Injection BP 300 mg/20 mL ampoule.
Dosage / Interval	5–15 mg/kg/day. Can be given as 2–5 mg/kg/dose every 8 hours or 2.5–7.5 mg/kg/dose every 12 hours.
Maximum daily dose	Neonates: 15 mg/kg/day. Children: Up to 30 mg/kg/day but caution exceeding 20 mg/kg/day.
Route	Oral. Intravenous.
Preparation/Dilution	Oral solution: Shake well before use. Intravenous: Do not dilute (15 mg/mL).
Administration	Oral: Administer after feeds (preferred). Intravenous: Administer over at least 30 seconds. DO NOT administer by intramuscular or subcutaneous injection (alkaline solution).
Monitoring	Monitor blood pressure and blood glucose levels during initial treatment. Monitor for sodium and fluid retention (urine output, electrolytes and weight). Consider monitoring albumin and liver function. ¹
Contraindications	Hypersensitivity to thiazide derivatives.
Precautions	Avoid sodium and water overload. Concomitant use of a thiazide diuretic is recommended. Avoid higher doses where possible. Use with caution in premature infants – increased risk of cardiorespiratory complications; Use with caution in jaundice – may displace bilirubin from albumin. Reduce dose in infants with renal impairment. Use with caution in infants with hepatic impairment. Use with caution in mechanical hypertension, e.g. secondary to aortic coarctation or arteriovenous shunt. Use with caution in pulmonary hypertension.
Drug Interactions	Concomitant administration of diuretics may result in potentiation of the hyperglycaemic, hyperuricaemic or hypotensive effect of diazoxide.
Adverse Reactions	Tolerance to diazoxide is usually good. Severe adverse effects include sodium and fluid retention which may precipitate congestive heart failure in patients with compromised cardiac reserve. Usually responds to diuretic therapy. Life-threatening episodes of pulmonary hypertension were observed in some neonates receiving diazoxide. ² Prematurity and higher diazoxide doses are risk factors for cardiovascular side effects. ³ Severe hypotension can be controlled with sympathomimetic agents if necessary. With prolonged use, hypertrichosis can sometimes be marked and distressing in young children, but will be reversible after treatment cessation. Haematological side effects are very rare with the usual doses.

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	Overdose of diazoxide produces hyperglycaemia and possibly ketoacidosis which should be treated promptly with insulin and restoration of fluid and electrolyte balance.
Compatibility	Do not mix with other fluids or drugs.
Incompatibility	Do not mix with other fluids or drugs.
Stability	Discard remaining IV solution after use.
Storage	Ampoules: Store below 25°C. Protect from light. Avoid excessive heat and freezing. Oral solution: As per advice from Pharmacy.
Special Comments	Concomitant use of a thiazide diuretic is recommended to counter sodium and fluid retention from use of diazoxide. ^{4,5} Oral diazoxide is not registered in Australia. Complete a category A Special Access Scheme form and obtain parental consent.
Evidence summary	Efficacy: There are no clinical trials of diazoxide for management of hyperinsulinaemic hypoglycaemia. Transient and syndromic hyperinsulinaemic hypoglycaemia tends to be diazoxide responsive, whereas other genetic forms affecting the K-ATP channel and incretin receptors, and infants with insulinomas, are variably responsive. ^{2-4,6-9} (LOE IV, GOR C) Pharmacokinetics: Not reported in newborns or children. Long half-life in adults (48 hours), 94% protein bound (albumin), and renally excreted. ^{10,11} Albumin binding and renal clearance of diazoxide reduced in renal failure. ¹² (LOE – none in infants) Safety: High rate of reported complications: Total 37%; circulatory complications 19%; oedema 17%; oliguria 5%; reopening of the ductus arteriosus 4%; hypertrichosis 15%; hyperkalaemia 4%; deterioration of liver function 1%; others 8%. ³ (LOE IV, GOR C). Overdose guideline: None found.
References	<ol style="list-style-type: none"> 1. Tas E, Mahmood B, Garibaldi L, Sperling M. Liver injury may increase the risk of diazoxide toxicity: a case report. <i>European journal of pediatrics</i>. 2015;174:403-6. 2. Arnoux JB, Verkarre V, Saint-Martin C, Montravers F, Brassier A, Valayannopoulos V, Brunelle F, Fournet JC, Robert JJ, Aigrain Y, Bellanne-Chantelot C, de Lonlay P. Congenital hyperinsulinism: current trends in diagnosis and therapy. <i>Orphanet journal of rare diseases</i>. 2011;6:63. 3. Yoshida K, Kawai M, Marumo C, Kanazawa H, Matsukura T, Kusuda S, Yorifuji T, Heike T. High prevalence of severe circulatory complications with diazoxide in premature infants. <i>Neonatology</i>. 2014;105:166-71. 4. Banerjee I, Avatapalle B, Padidela R, Stevens A, Cosgrove KE, Clayton PE, Dunne MJ. Integrating genetic and imaging investigations into the clinical management of congenital hyperinsulinism. <i>Clinical endocrinology</i>. 2013;78:803-13. 5. Senniappan S, Shanti B, James C, Hussain K. Hyperinsulinaemic hypoglycaemia: genetic mechanisms, diagnosis and management. <i>Journal of inherited metabolic disease</i>. 2012;35:589-601. 6. Padidela R, Fiest M, Arya V, Smith VV, Ashworth M, Rampling D, Newbould M, Batra G, James J, Wright NB, Dunne MJ, Clayton PE, Banerjee I, Hussain K. Insulinoma in childhood: clinical, radiological, molecular and histological aspects of nine patients. <i>European journal of endocrinology / European Federation of Endocrine Societies</i>. 2014;170:741-7. 7. Hu S, Xu Z, Yan J, Liu M, Sun B, Li W, Sang Y. The treatment effect of diazoxide on 44 patients with congenital hyperinsulinism. <i>Journal of pediatric endocrinology & metabolism : JPEM</i>. 2012;25:1119-22. 8. Flanagan SE, Patch AM, Locke JM, Akcay T, Simsek E, Alaei M, Yekta Z, Desai M, Kapoor RR, Hussain K, Ellard S. Genome-wide homozygosity analysis reveals HADH mutations as a common cause of diazoxide-responsive hyperinsulinemic-hypoglycemia in consanguineous pedigrees. <i>The Journal of clinical endocrinology and metabolism</i>. 2011;96:E498-502. 9. Shi Y, Avatapalle HB, Skae MS, Padidela R, Newbould M, Rigby L, Flanagan SE, Ellard S, Rahier J, Clayton PE, Dunne MJ, Banerjee I, Cosgrove KE. Increased plasma incretin concentrations identifies a subset of patients with persistent congenital hyperinsulinism

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Original version Date: 6/10/2016	Author: NMF Consensus Group
Current Version number: 1	Current Version Date: 6/10/2016
Risk Rating: High	Due for Review: 6/10/2018
Approval by: As per Local policy	Approval Date: