Diazoxide

Section: 18. Medicines for endocrine disorders > 18.6. Medicines for hypoglycaemia

EMLc | ATC codes: V03AH01

Indication	Persistent hyperinsulinaemic hypoglycaemia of infancy ICD11 code: 5A45
INN	Diazoxide
Medicine type	Chemical agent
List type	Complementary
Formulations	**Oral > Liquid:** 50 mg per mL (EMLc) **Oral > Solid:** 50 mg (EMLc)
EML status history	First added in 2019 (TRS 1021)
Sex	All
Age	Children (1 month - 12 years)
Therapeutic alternatives	The recommendation is for this specific medicine
Patent information	Patents have expired in most jurisdictions Read more about patents.
Wikipedia	Diazoxide
DrugBank	Diazoxide

Expert Committee recommendation

The Committee recommended the addition of diazoxide to the complementary list of the EMLc for the management of hypoglycaemia secondary to prolonged hyperinsulinism (HI), based on evidence of favourable efficacy and tolerability, and taking into account the serious consequences of this condition in children not treated. The Committee noted the variable global availability and reliability of supply of diazoxide and considered inclusion of diazoxide on the EMLc could help to facilitate more reliable access.

Background

The application requested the inclusion of diazoxide on the EMLc for the management of hypoglycaemia secondary to prolonged hyperinsulinism (HI). Diazoxide had not previously been considered for inclusion on the EMLc for this indication.

Public health relevance

Congenital hyperinsulinism (HI) disorders are a group of disorders characterized by inappropriately persistent secretion of insulin in the context of low blood glucose. This condition can be transient or permanent. It is responsible for permanent neurological damage in the newborn and infant. Congenital HI has an estimated incidence ranging from 1 in 50 000 live births, with considerably higher incidence (up to 1 in 2500) seen in populations with high rates of consanguineous unions (1). Recurrent episodes of hypoglycaemia produced by HI increase risk for seizures, brain damage and intellectual disability. Management of hypoglycaemia is critical to prevent and reduce the risk of these serious consequences (2). Neurological damage is present in up to 50% of children with early onset HI. Neurodevelopmental damage is observed in transient, permanent, mild and severe

forms of HI, emphasizing the need for rapid diagnosis and prompt management (3–6). Diazoxide is indicated for hypoglycaemia that is secondary to transient and prolonged inappropriate insulin secretion and as a first-line treatment in patients with permanent HI where a dietary approach alone does not appropriately prevent hypoglycaemia.

Benefits

No randomized controlled trials involving diazoxide were identified in the application. Case series studies from China (7), Germany (5), Turkey (8, 9), Thailand (10) and the United Kingdom (11) have reported the clinical response to diazoxide therapy ranging from 40% to 74% at dose ranges up to 20 mg/kg/day. The effect of diazoxide depends on the genetic cause of hyperinsulinism. The majority of cases of neonatal onset persistent congenital HI are caused by defects in the KATP channel genes of the beta-cell of the pancreas, and diazoxide is ineffective in these patients (12).

Harms

The total number of patients who have received diazoxide to date has not been assessed. It is estimated that tens of thousands of patients have received diazoxide since 1964. The application summarized safety findings for diazoxide from cohort studies and case reports (5, 7, 13–24). The medicine is usually well tolerated. Adverse effects include water retention and hyponatraemia at onset of therapy, and hypertrichosis (in particular on back and limbs) that is reversible after the treatment is discontinued. Less commonly reported adverse events include rash, thrombocytopenia, neutropenia, heart failure, extrapyramidal adverse events and paradoxical hypoglycaemia. Adverse events may be dose-related and are usually reversible with dose reduction or discontinuation of therapy. Heart failure secondary to water retention has been reported in premature babies and associated with reopening of the ductus arteriosus. Diazoxide is recommended to be used with caution in these patients (13). Pulmonary hypertension has been reported to the United States Food and Drug Administration and Health Canada in neonates and infants treated with diazoxide. The application noted that overall, the quality of the safety data is weak as it comes from small series of patients and case reports. No randomized controlled trials are available. Adverse events data was not systematically collected in the cohort studies. The likelihood that adverse events were associated with diazoxide was not assessed in any of the cohort studies or case reports.

Additional evidence

A retrospective cohort study of 295 patients investigated the prevalence of adverse events in children with congenital HI treated with diazoxide (25). 2.4% of children developed pulmonary hypertension after initiation of diazoxide (most of them had additional risk factors such as prematurity, structural heart disease and respiratory failure). In addition, 15.6% developed neutropenia, 4.7% thrombocytopenia and 5% hyperuricaemia. The authors concluded that screening for neutropenia, thrombocytopenia and hyperuricaemia in diazoxide-treated patients may be of value given the relatively high prevalence of these events.

Cost / cost effectiveness

No information was provided in the application regarding the cost and cost-effectiveness of diazoxide. Preliminary results of an international survey of paediatric endocrinologists conducted in 2018 by Congenital Hyperinsulinism International to assess the availability and need for diazoxide reported that 53% of respondents agreed that cost to the patient was an obstacle to accessing diazoxide.

WHO guidelines

The 2013 WHO Pocket book of Hospital Care for Children (26) recognizes the importance of hypoglycaemia and the need to treat it as an emergency in order to prevent neurological sequelae. It focuses on the most common causes of hypoglycaemia and does not consider HI or make recommendations regarding diazoxide treatment. Clinical practice guidelines for congenital HI developed by the The Japanese Society for Pediatric Endocrinology and The Japanese Society of Pediatric Surgeons (12) make the following recommendations for first-line treatment

of congenital HI: • Maintain blood glucose above the target range by continuous glucose infusion. [Recommendation level 1, Evidence level A]. • When blood glucose is successfully maintained by continuous glucose infusion, nutritional support by frequent feeding, continuous feeding, cornstarch (after nine months), or formula for glycogen storage diseases should be attempted. [Recommendation level 1, Evidence level A]. • When blood glucose is not maintained by continuous glucose infusion, or when it is difficult to withdraw glucose infusion for an extended period, a 5-day trial of oral diazoxide, in 2–3 divided doses, at 5–15 mg/kg/day should be attempted, unless contraindicated by cardiac failure or pulmonary hypertension. [Recommendation level 1, Evidence level A]. • When diazoxide is effective in stabilizing blood glucose levels, intravenous glucose infusion should be withdrawn and transfer to nutritional support (frequent feeding, continuous feeding, or cornstarch formula for glycogen storage diseases) should be attempted. [Recommendation level 1, Evidence level A]. • While on diazoxide, the patient should be on a glucose self-monitoring regimen to detect episodes of hypoglycaemia. Furthermore, complete blood count (CBC), blood chemistry, and physical examination should be performed to detect frequent adverse events, such as hypertrichosis, tachycardia, or oedema. [Recommendation level 1, Evidence level B]. • When euglycaemia is not achieved by the first line treatment and continuous glucose infusion cannot be withdrawn, the second-line treatment should be initiated. [Recommendation level 1, Evidence level A].

Availability

Global availability, although reliable supply and regulatory approval of diazoxide is variable.

Other considerations

Comments on the applications were received from the WHO department of Management of NCDs, Disability, Violence and Injury Prevention. The technical unit advised that it supported the addition of diazoxide to the complementary list of the EMLc, stating that congenital hyperinsulinism is a rare but serious condition requiring specialist assessment and care, and that inclusion of diazoxide on the EMLc could facilitate access to this medicine in countries where it is currently unavailable.

1. Arnoux JB, Verkarre V, Saint-Martin C, Montravers F, Brassier A, Valayannopoulos V et al. Congenital hyperinsulinism: current trends in diagnosis and therapy. Orphanet J Rare Dis. 2011;6:63.
2. Hussain K, Blankenstein O, De Lonlay P, Christesen HT. Hyperinsulinaemic hypoglycaemia: biochemical basis and the importance of maintaining normoglycaemia during management. Arch Dis Child. 2007;92(7):568–70.
3. Avatapalle HB, Banerjee I, Shah S, Pryce M, Nicholson J, Rigby L et al. Abnormal Neurodevelopmental Outcomes are Common in Children with Transient Congenital Hyperinsulinism. Front Endocrinol (Lausanne). 2013;4:60.
4. Ludwig A, Ziegenhorn K, Empting S, Meissner T, Marquard J, Holl R et al. Glucose metabolism and neurological outcome in congenital hyperinsulinism. Semin Pediatr Surg. 2011;20(1):45–9.
5. Meissner T, Wendel U, Burgard P, Schaetzle S, Mayatepek E. Long-term follow-up of 114 patients with congenital hyperinsulinism. Eur J Endocrinol. 2003;149(1):43–51.
6. Menni F, de Lonlay P, Sevin C, Touati G, Peigne C, Barbier V et al. Neurologic outcomes of 90 neonates and infants with persistent hyperinsulinemic hypoglycemia. Pediatrics. 2001;107(3):476–9.
7. Gong C, Huang S, Su C, Qi Z, Liu F, Wu D et al. Congenital hyperinsulinism in Chinese patients: 5-yr treatment outcome of 95 clinical cases with genetic analysis of 55 cases. Pediatr Diabetes. 2016;17(3):227–34.
8. Guven A, Cebeci AN, Ellard S, Flanagan SE. Clinical and Genetic Characteristics, Management and Long-Term Follow-Up of Turkish Patients with Congenital Hyperinsulinism. J Clin Res Pediatr Endocrinol. 2016;8(2):197–204.
9. Demirbilek H, Arya VB, Ozbek MN, Akinci A, Dogan M, Demirel F et al. Clinical characteristics and phenotype-genotype analysis in Turkish patients with congenital hyperinsulinism; predominance of recessive KATP channel mutations. Eur J Endocrinol. 2014;170(6):885–92.
10. Sawathiparnich P, Likitmaskul S, Angsusingha K, Nimkarn S, Chaichanwatanakul K, Laohapansang M et al. Persistent hyperinsulinemic hypoglycemia of infancy: experience at Siriraj Hospital. J Med Assoc Thai. 2002;85 Suppl 2:S506–12.
11. Banerjee I, Skae M, Flanagan SE, Rigby L, Patel L, Didi M et al. The contribution of rapid KATP channel gene mutation analysis to the clinical management of children with congenital hyperinsulinism. Eur J Endocrinol. 2011;164(5):733–40.
12. Yorifuji T, Horikawa R, Hasegawa T, Adachi M, Soneda S, Minagawa M et al. Clinical practice guidelines for congenital hyperinsulinism. Clin Paediatr Endocrinol. 2017;26(3):127–52.
13. Yoshida K, Kawai M, Marumo C, Kanazawa H, Matsukura T, Kusuda S et al. High prevalence of severe circulatory complications with diazoxide in premature infants. Neonatology. 2014;105(3):166–71.
14. Hu S, Xu Z, Yan J, Liu M, Sun B, Li W et al. The treatment effect of diazoxide on 44 patients with congenital hyperinsulinism. J Pediatr Endocrinol Metab. 2012;25(11–12):1119–22.
15. Touati G, Poggi-Travert F, Ogier de Baulny H, Rahier J, Brunelle F, Nihoul-Fekete C et al. Long-term treatment of persistent hyperinsulinaemic hypoglycaemia of infancy with diazoxide: a retrospective review of 77 cases and analysis of efficacy-predicting criteria. Eur J Pediatr. 1998;157(8):628–33.

16. Abu-Osba YK, Manasra KB, Mathew PM. Complications of diazoxide treatment in persistent neonatal hyperinsulinism. Arch Dis Child. 1989;64(10):1496–500.
17. Goode PN, Farndon JR, Anderson J, Johnston ID, Morte JA. Diazoxide in the management of patients with insulinoma. World J Surg. 1986;10(4):586–92.
18. Silvani P, Camporesi A, Mandelli A, Wolfler A, Salvo I. A case of severe diazoxide toxicity. Paediatr Anaesth. 2004;14(7):607–9.
19. Parker JJ, Allen DB. Hypertrophic cardiomyopathy after prolonged diazoxide therapy for hyperinsulinemic hypoglycemia. J Pediatr. 1991;118(6):906–9.
20. Combs JT, Grunt JA, Brandt IK. Hematologic reactions to diazoxide. Pediatrics. 1967;40(1):90-2.
21. McGraw ME, Price DA. Complications of diazoxide in the treatment of nesidioblastosis. Arch Dis Child. 1985;60(1):62–4.
22. Ponmani C, Gannon H, Hussain K, Senniappan S. Paradoxical hypoglycaemia associated with diazoxide therapy for hyperinsulinaemic hypoglycaemia. Horm Res Paediatr. 2013;80(2):129–33.
23. Darendeliler F, Bundak R, Bas F, Saka N, Gunoz H. Long-term diazoxide treatment in persistent hyperinsulinemic hypoglycemia of infancy: a patient report. J Pediatr Endocrinol Metab. 1997;10(1):79–81.
24. Tas E, Mahmood B, Garibaldi L, Sperling M. Liver injury may increase the risk of diazoxide toxicity: a case report. Eur J Pediatr. 2015;174(3):403–6.
25. Herrera A, Vajravelu ME, Givler S, Mitteer L, Avitabile CM, Lord K et al. Prevalence of Adverse Events in Children With Congenital Hyperinsulinism Treated With Diazoxide. J Clin Endocrinol Metab. 2018;103(12):4365–72.
26. Pocket book of hospital care for children: guidelines for the managment of common illnesses with limited resources. Geneva: World Health Organization; 2013. Available from https://www.who.int/maternal_child_adolescent/documents/9241546700/en/, accessed 30 October 2019.

