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Treatment of hyperinsulinaemic hypoglycaemia with nifedipine

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Abstract We report on two children with mild persistent hyperinsulinaemic hypoglycaemia. In both, oral nifedipine treatment (0.7 and 2.0 mg/kg per day respectively) had a significant clinical effect. In one case, nifedipine monotherapy prevented hypoglycaemia; in the second case, the dosage and the side-effects of other substances could be reduced, thus circumventing surgical therapy.

Conclusion Nifedipine treatment has a favourable effect on the clinical course of patients with mild hyperinsulinism. It represents a valuable new substance for the treatment of this disorder.

Key words Nifedipine · Hypoglycemia · Hyperinsulinism · Nesidioblastosis · Persistent hyperinsulinaemic hypoglycaemia of infancy

Abbreviation PHHI persistent hyperinsulinaemic hypoglycaemia of infancy

Introduction

Persistent hyperinsulinaemic hypoglycaemia of infancy (PHHI) is a rare, heterogeneous disorder of glucose metabolism affecting approximately 1 in 50000 individuals [1, 6]. PHHI presents with variable clinical phenotype including cases with mild or very severe hypoglycaemia. Since the risk of neurological damage is high, early diagnosis and appropriate treatment have a pivotal role in long-term outcome. Although a surgical management is frequently required, some milder cases respond to a protein-restricted diet and/or to medical treatment with diazoxide or/and the somatostatin analogue octreotide [4]. However, side-effects of these drugs such as anorexia, nausea, vomiting, fluid retention with oedema, and hypertrichosis are limiting factors and in many cases surgical treatment cannot be circumvented. Here we report on two children with hyperinsulinaemic hypoglycaemia with a favourable response to the calcium channel blocker nifedipine.

Case reports

Case 1

The female patient is the first child of non-consanguineous German parents. Pregnancy, birth (birth weight 4050 g) and the first months of life were uneventful. At the age of 6 months, a generalized seizure during hypoglycaemia (plasma glucose level 13 mg/dl) occurred with subsequent recurrent episodes of spontaneous hypoglycaemia. Hyperinsulinism was suspected because hypoketotic hypoglycaemia could not be prevented by intravenous glucose (9 mg/kg per min) in addition to oral feeding with 120–140 kcal/kg per day. Repeatedly, an increased insulin [$\mu\text{U/l}$]/glucose [mg/dl]-ratio (max. 0.98 (normal < 0.4)) was documented. Ultrasound and CT scans did not show any focal pancreatic lesions.

Medical treatment with diazoxide was initiated and prevented hypoglycaemia at a dosage of 10 mg/kg per day. However, anorexia and vomiting made oral feedings impossible and infusion therapy was still necessary. Therefore, a therapeutic trial with nifedipine (0.7 mg/kg per day) was started. Plasma glucose concentration increased somewhat but termination of intravenous glucose infusions was not possible. A combined drug therapy with

nifedipine (0.7 mg/kg per day) and diazoxide in a reduced dose (6 mg/kg per day) was therefore introduced and was effective. Glucose infusion could be terminated without the recurrence of hypoglycaemia (Fig. 1a,b). With the exception of tolerable hypertrichosis, the side-effects of diazoxide disappeared and this therapy has been continued for more than 2 years. Before discharge from hospital the parents were instructed to monitor the child's blood glucose (with a minimum of three and up to 12 determinations per day). Repeatedly, a decline in plasma glucose level, without reaching hypoglycaemic levels, has been observed. This could be reversed by an adjustment of the drug dosage to the increasing body weight, suggesting that hyperinsulinism is persistently present.

Case 2

This patient is the second child of non-consanguineous German parents. Her mother, the maternal grandmother, and a maternal aunt also suffer from persistent hypoglycaemia suggesting a dominant trait [3]. An activating mutation in exon 10 of the glucokinase gene as reported by Glaser et al. [2] was not detectable. The girl was born at term with a birth weight of 2800 g. During the newborn period tetralogy of Fallot was diagnosed. At that time no hypoglycaemia was noted. At the age of 15 months the patient had a first hypoglycaemic seizure (plasma glucose 36 mg/dl). Since the age of 19 months hypoketotic hypoglycaemia with a minimum plasma glucose concentration of 16 mg/dl was repeatedly documented during periods of prolonged fasting and after protein-rich feeds. During hypoglycaemic episodes, plasma insulin concentration was repeatedly elevated up to a value of 16.9 μ U/ml. Consequently, the insulin [μ U/ml]/glucose [mg/dl]-ratio was elevated (0.54 normal < 0.4). An oral provocation test with leucine (150 mg/kg) resulted in severe hypoglycaemia with an inappropriately high insulin/glucose-ratio of 0.9. Since the patient's mentally retarded mother was considered to be unable to prepare a protein-restricted diet with frequent feeds, medical treatment was started. After increasing oral monotherapy with nifedipine to a dosage of 2 mg/kg per day, no further episodes of hypoglycaemia could be documented (Fig. 1c,d).

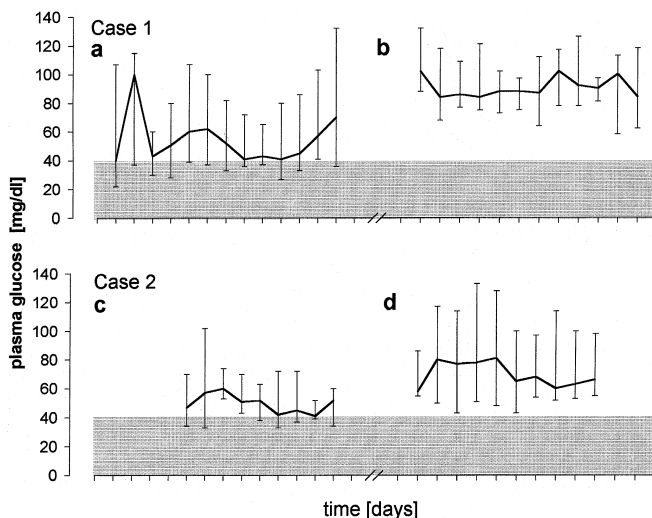


Fig. 1a-d Daily median and range of plasma glucose (minimum six determinations) in cases 1 (a,b) and 2 (c,d) before and after the introduction of nifedipine. **a** Case 1 on additional iv glucose (9 mg/kg per min), no medication; **b** case 1, without additional parenteral glucose, diazoxide (6 mg/kg per day), nifedipine (0.7 mg/kg per day); **c** case 2, no medication; **d** case 2, nifedipine (2 mg/kg per day) (for details see text)

Discussion

The metabolic steps coupling plasma glucose levels to insulin secretion have been largely elucidated [7]. An increase of plasma glucose results in an increased uptake and metabolism of glucose by β -cells. The consecutive change in the intracellular ATP/ADP ratio can be sensed by potassium channels resulting in a diminished conductivity and a depolarisation of the cell membrane. Mutations in genes for the glucose metabolizing enzyme glucokinase, for glutamate dehydrogenase and for different subunits of the ATP-sensitive potassium channels have recently been found in patients with PHHI [2, 8–10]. Insulin liberation from β -cells is then coupled to the depolarisation of the cell membrane by the intracellular calcium concentration regulated by voltage-dependent L-type calcium channels.

Although the mechanisms causing hyperinsulinism are not yet clear in our patients, the increased calcium influx is the common signalling pathway for all types of congenital hyperinsulinism. To date, there is one single report by Lindley et al. who demonstrated that calcium channel blockers can principally reduce inappropriately high insulin secretion [5]. According to in vitro and in vivo studies in a patient with severe hyperinsulinism, insulin secretion was inhibited but nifedipine therapy was not sufficient to prevent hypoglycaemia necessitating surgical treatment.

The two cases reported here differ from the case of Lindley et al. in that the use of nifedipine changed the clinical course. In one patient, hypoglycaemia subsided on nifedipine monotherapy and in the other diazoxide could be reduced alleviating side-effects. Surgical treatment was unnecessary. Both patients were carefully monitored for arterial hypotension and the development of tachycardia as well as the occurrence of peripheral oedema. Neither these nor other side-effects such as dizziness, nausea, flushing or abnormal laboratory tests known to be associated with nifedipine therapy have been observed.

The difference in the response to nifedipine treatment in our cases and that of Lindley et al. described earlier is probably explained by the milder degree of hyperinsulinism in our patients. We therefore conclude that nifedipine is a valuable, comparably well-tolerated substance for the medical treatment of hyperinsulinism, particularly for mild cases.

References

1. Bruining GJ (1992) Recent advances in hyperinsulinism and the pathogenesis of diabetes mellitus. *Curr Opin Pediat* 2:758–765
2. Glaser B, Kesavan P, Heyman M, Davis E, Cuesta A, Buchs A, Stanley CA, Thornton PS, Permutt MA, Matschinsky FM, Herold KC (1998) Familial hyperinsulinism caused by an activating glucokinase mutation. *N Engl J Med* 338:226–230
3. Hufnagel M, Eichmann D, Stieh J, Santer R (1998) Further evidence for a dominant form of familial persistent hyper-

- insulinemic hypoglycemia of infancy: a family with documented hyperinsulinemia in two generations. *J Clin Endocrinol Metab* 83:2215–2216
4. Kane C, Lindley KJ, Johnson PRV, James RFL, Milla PJ, Aynsley-Green A, Dunne MJ (1997) Therapy for persistent hyperinsulinemic hypoglycemia of infancy. Understanding the responsiveness of beta cells to diazoxide and somatostatin. *J Clin Invest* 100:1888–1893
 5. Lindley KJ, Dunne MJ, Kane C, Shepherd RM, Squires PE, James RFL, Johnson PRV, Eckhardt S, Wakeling E, Dattani M, Milla PJ, Aynsley-Green A (1996) Ionic control of β -cell function in nesidioblastosis: A possible therapeutic role for calcium channel blockade. *Arch Dis Child* 74:373–378
 6. Milner RD (1996) Nesidioblastosis unravelled. *Arch Dis Child* 74:369–372
 7. Newgard CB, McGarry JD (1995) Metabolic coupling factors in pancreatic beta-cell signal transduction. *Annu Rev Biochem* 64:689–719
 8. Stanley CA, Lieu YK, Hsu BYL, Burlina AB, Greenberg CR, Hopwood NJ, Perlman K, Rich BH, Zammarchi E, Poncz M (1998) Hyperinsulinism and hyperammonemia in infants with regulatory mutations of the glutamate dehydrogenase gene. *N Engl J Med* 338:1352–1357
 9. Thomas P, Cote, GJ, Wohlk N, Haddad B, Mathew PM, Rabl W, Aguilar-Bryan L, Gagel RF, Bryan J (1995) Mutations in the sulfonylurea receptor gene in familial persistent hyperinsulinemic hypoglycemia of infancy. *Science* 268:426–429
 10. Thomas P, Ye Y, Lightner E (1996) Mutation of the pancreatic islet inward rectifier Kir6.2 also leads to familial persistent hyperinsulinemic hypoglycemia of infancy. *Hum Molec Genet* 5:1809–1812

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