

Sulfonylurea Treatment in Young Children with Neonatal Diabetes: Dealing with Hyperglycaemia, Hypoglycaemia and Sickdays

Received for publication 16 October 2006 and accepted in revised form 26 January 2007.

Running title: Sulfonylureas in neonatal diabetes

Ethel Codner, MD¹, Sarah E. Flanagan BSc², Francisca Ugarte, MD³, Hernán García, MD⁴, Teresa Vidal, MD⁵, Sian Ellard PhD² MRCPath, Andrew T. Hattersley, DM, FRCP².

¹: Institute of Maternal and Child Research, School of Medicine, University of Chile, Santiago, Chile;

²: Institute of Biomedical and Clinical Science, Peninsula Medical School, Exeter, United Kingdom;

³: Hospital Exequiel González Cortés, Santiago, Chile.

⁴: Clínica Santa María, Santiago, Chile.

⁵: Hospital Dr. Hernán Henríquez, Temuco, Chile.

Corresponding author:

Prof. Andrew T. Hattersley,

Institute of Biomedical and Clinical Science,

Peninsula Medical School,

Barrack Rd.,

Exeter EX2 5DW,

United Kingdom

Email: A.T.Hattersley@ex.ac.uk

Telephone: +44 1392 406807

Fax: +44 1392 406767:

Recently, heterozygous activating mutations in the genes forming the ATP-sensitive potassium channel, *KCNJ11* and *ABCC8*, have been shown to cause neonatal diabetes (1-4). Sulfonylurea treatment restores insulin secretion in these patients (3; 5; 6) but information on the practical management of children with mutated K_{ATP} channels taking this medication is limited.

We report clinical aspects of the successful transfer to oral treatment in three cases of young children with *KCNJ11* and *ABCC8* mutations (Table 1). All the parents gave written consent.

Case 1. This girl was transferred from insulin to glibenclamide at 17 months (7), and has been on this treatment for two years. During this period blood glucose (BG) testing decreased from 5-6 to 2-3 tests/day. As BG levels were not affected by the ingestion of different amounts of carbohydrates, a free diet was initiated. Unexplained hyperglycemia episodes were occasionally observed and an appropriate decrease in the BG level was observed with the usual dose of glibenclamide, even in the face of hyperglycemia of 350 mg/dl. When the parents missed one dose, BG was 455 mg/dl without ketosis which was treated at home with lispro insulin dose and administration of the missed sulfonylurea dose. Only one episode of symptomatic hypoglycemia (30 mg/dl) occurred and was successfully treated with fruit juice and a temporary decrease in glibenclamide.

Minor episodes of viral respiratory disease were managed by decreasing the sulfonylurea dose to avoid hypoglycaemia. One episode of rotavirus diarrhea was managed in hospital using insulin and stopping glibenclamide. Upon discharge, the sulfonylurea was restarted at the

previous dose. Ketones were not detected on any of these acute illnesses.

Case 2. This boy with a *KCNJ11* mutation was successfully transferred from insulin to glibenclamide at 38 months. This patient also had some episodes of unexpected hyperglycemia which responded to taking the normal glibenclamide dose. An episode of a febrile upper respiratory tract viral illness was managed with a decrease of the glibenclamide dose, ketones were not detected and insulin was not required.

Case 3. This girl was treated with insulin until the confirmation of a novel mutation in *ABCC8* when aged three years. Unexpectedly, a low dose of glibenclamide (0.1 mg/kg/day) not only allowed the stopping of insulin but also resulted in episodes of asymptomatic hypoglycemia. The dose was reduced and then discontinued completely for 12 days, but as hyperglycemia recurred tolbutamide was begun resulting in good control without hypoglycaemia.

These cases show that the use of sulphonylureas in children with K_{ATP} mutations differ from adults with T2D. In 2 cases glibenclamide was best given three times a day. These children also required a higher night-time dose to lower morning glucose, possibly as sulphonylureas act through facilitating the response to incretins in this type of diabetes (5). Sulfonylurea treatment was well tolerated, however, the risk of hypo and hyperglycemia persists so education in their prevention and treatment should be given. Hyperglycemia, even 350 mg/dl, responded to the usual dose of sulfonylureas, but if these patients consistently miss medication they risk ketoacidosis.

Acknowledgments: This work was supported in part by the Fondo Nacional de Desarrollo Científico y Tecnológico, Chile (FONDECYT) grant N° 1050452 to EC and by the Wellcome Trust. We are grateful to Dr. María Isabel Hernández

and Mrs. Alejandra Ávila, BSc, from the Institute of Maternal and Child Research, University of Chile, Santiago, Chile for their help in the care of these patients.

References

1. Gloyn AL, Pearson ER, Antcliff JF, Proks P, Bruining GJ, Slingerland AS, Howard N, Srinivasan S, Silva JMCL, Molnes J, Edghill EL, Frayling TM, Temple IK, Mackay D, Shield JPH, Sumnik Z, van Rhijn A, Wales JKH, Clark P, Gorman S, Aisenberg J, Ellard S, Njolstad PR, Ashcroft FM, Hattersley AT: Activating Mutations in the Gene Encoding the ATP-Sensitive Potassium-Channel Subunit Kir6.2 and Permanent Neonatal Diabetes. *N Engl J Med* 350:1838-1849, 2004
2. Proks P, Arnold AL, Bruining J, Girard C, Flanagan SE, Larkin B, Colclough K, Hattersley AT, Ashcroft FM, Ellard S: A heterozygous activating mutation in the sulphonylurea receptor SUR1 (ABCC8) causes neonatal diabetes. *Hum Mol Genet*, 15, 1793-800, 2006
3. Babenko AP, Polak M, Cave H, Busiah K, Czernichow P, Scharfmann R, Bryan J, Aguilar-Bryan L, Vaxillaire M, Froguel P: Activating Mutations in the ABCC8 Gene in Neonatal Diabetes Mellitus. *N Engl J Med* 355:456-466, 2006
4. Hattersley AT, Ashcroft FM: Activating Mutations in Kir6.2 and Neonatal Diabetes: New Clinical Syndromes, New Scientific Insights, and New Therapy. *Diabetes* 54:2503-2513, 2005
5. Pearson ER, Flechtner I, Njolstad PR, Malecki MT, Flanagan SE, Larkin B, Ashcroft FM, Klimes I, Codner E, Iotova V, Slingerland AS, Shield J, Robert J-J, Holst JJ, Clark PM, Ellard S, Sovik O, Polak M, Hattersley AT, the Neonatal Diabetes International Collaborative Group: Switching from Insulin to Oral Sulfonylureas in Patients with Diabetes Due to Kir6.2 Mutations. *N Engl J Med* 355:467-477, 2006
6. Sagen JV, Raeder H, Hathout E, Shehadeh N, Gudmundsson K, Baevre H, Abuelo D, Phornphutkul C, Molnes J, Bell GI, Gloyn AL, Hattersley AT, Molven A, Sovik O, Njolstad PR: Permanent Neonatal Diabetes due to Mutations in KCNJ11 Encoding Kir6.2: Patient Characteristics and Initial Response to Sulfonylurea Therapy. *Diabetes* 53:2713-2718, 2004
7. Codner E, Flanagan S, Ellard S, Garcia H, Hattersley AT: High-Dose Glibenclamide Can Replace Insulin Therapy Despite Transitory Diarrhea in Early-Onset Diabetes Caused by a Novel R201L Kir6.2 Mutation. *Diabetes Care* 28:758-759, 2005

Table: Clinical and molecular study of the three children with early onset diabetes mellitus, as well as information about their sulfonylureas treatment.

Case	1	2	3
Molecular study	R201L in <i>KCNJ11</i>	R201H in <i>KCNJ11</i>	Q211K in <i>ABCC8</i>
Age DM was diagnosed (months)	4	6	4
Ketoacidosis at onset	+	+	+
Insulin dose before sulfonylurea treatment (U/Kg/day)	0.6	0.7	0.3
Type of insulin used	Glargine/lispro	NPH/lispro	Glargine/lispro
HbA1c before sulfonylurea treatment	7.3	8.9	6.7
Sulfonylureas treatment that allowed stopping insulin			
Age sulfonylurea treatment was begun (yr)	1.4	3.1	3
Drug used for successful transfer	Glibenclamide	Glibenclamide	Glibenclamide
Dose (mg/kg/day)	0.8	0.6	0.3
Number of doses/day	2	3	2
Dose (mg/dose)	3.75 - 3.75	2.5 - 3.0 -3.5	1.5 - 1.5
Sulfonylureas treatment at the last medical visit			
Drug used at the last medical visit	Glibenclamide	Glibenclamide	Tolbutamide
Duration of sulfonylureas treatment (months)	26.0	5.0	4.5
Dose (mg/kg/day)	0.3	0.6	1.4
Number of doses/day	3	3	1
Dose (mg/dose)	0.75 -1.25 - 2.25	2.25 - 2.75 - 3.75	15.6
HbA1c during sulfonylureas treatment	5.0-6.5	5.8	6.8
Medical problems observed during sulfonylureas treatment			
	Initial diarrhea	Sick management	day Hypoglycemia with low doses of glibenclamide
	Unexplained hyperglycemia	Unexplained occasional hyperglycemia	Transient diarrhea with glibenclamide
	Hyperglycemia associated with missed dose		
	Hypoglycemia		
	Sick management	day	

