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

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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.

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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 sulfonylureas 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.

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Table 1

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 *KCNJ11*	R201H in *KCNJ11*	Q211K in *ABCC8*
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 Unexplained hyperglycemia Hyperglycemia associated with missed dose Hypoglycemia Sick day management	Sick day management Unexplained occasional Hyperglycemia	Hypoglycemia with low doses of glibenclamide Transitory diarrhea with glibenclamide