OBSERVATIONS

Sulfonylurea Treatment in Young Children With Neonatal Diabetes

Dealing with hyperglycemia, hypoglycemia, and sick days

Recently, heterozygous activating mutations in the genes forming the ATP-sensitive K^+ channel (K_{ATP} 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 parents gave written consent.

In case 1, a girl was transferred from insulin to glibenclamide at 17 months (7) and had been on this treatment for 2 years. During this period, blood glucose testing decreased from 5–6 to 2–3 tests/day. As blood glucose levels were not affected by the ingestion of different amounts of carbohydrates, a free diet was initiated. Unexplained episodes of hyperglycemia were occasionally observed, and an appropriate decrease in the blood glucose level was observed with the usual dose of glibenclamide, even in cases of hyperglycemia (blood glucose 350 mg/dl). When the parents missed one dose, blood glucose 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 hypoglycemia. One episode of rotavirus diarrhea was managed in a hospital using insulin and by stopping glibenclamide. Upon discharge, the sulfonylurea was restarted at the previous dose. Ketones were not detected on any of these acute illnesses.

In case 2, a 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, and ketones were not detected and insulin was not required.

In case 3, a girl was treated with insulin until the confirmation of a novel mutation in *ABCC8* when aged 3 years. Unexpectedly, a low dose of glibenclamide (0.1 $mg \cdot kg^{-1} \cdot day^{-1}$) 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. However, as hyperglycemia recurred tolbutamide was started, which resulted in good control without hypoglycemia.

These cases show that the use of sulfonylureas in children with K_{ATP} mutations differ from adults with type 2 diabetes. In two cases, glibenclamide was

Table 1—*Clinical and molecular study of the three children with early-onset diabetes and information about their sulfonylureas treatment*

Case	1	2	3
Molecular study	R201L in *KCNJ11*	R201H in *KCNJ11*	Q211K in *ABCC8*
Age diabetes was diagnosed (months)	4	6	4
Ketoacidosis at onset	+	+	+
Insulin dose before sulfonylurea treatment ($units \cdot kg^{-1} \cdot day^{-1}$)	0.6	0.7	0.3
Type of insulin used	Glargine/lispro	Isophane/lispro	Glargine/lispro
A1C before sulfonylurea treatment (%)	7.3	8.9	6.7
Sulfonylureas treatment that allowed stopping insulin			
Age sulfonylurea treatment began (years)	1.4	3.1	3
Drug used for successful transfer	Glibenclamide	Glibenclamide	Glibenclamide
Dose ($mg \cdot kg^{-1} \cdot day^{-1}$)	0.8	0.6	0.3
Doses/day (*n*)	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
Quantity/day ($mg \cdot kg^{-1} \cdot day^{-1}$)	0.3	0.6	1.4
Doses/day (*n*)	3	3	1
Quantity/dose (mg/dose)	0.75, 1.25, 2.25	2.25, 2.75, 3.75	15.6
A1C 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 Sick day management	Sick day management Unexplained occasional hyperglycemia	Hypoglycemia with low doses of glibenclamide Transitory diarrhea with glibenclamide

best given three times a day. These children also required a higher nighttime 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, and education in their prevention and treatment should be given. Hyperglycemia, even at blood glucose level 350 mg/dl, responded to the usual dose of sulfonylureas, but if these patients consistently miss medications they risk ketoacidosis.

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