

Improved long-term glucose control in neonatal diabetes mellitus after early sulfonylurea allergy

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Abstract

Background: Activating mutations of the *ABCC8* gene can lead to permanent neonatal diabetes mellitus (PNDM). Glucose variability in infants with NDM treated with insulin can be extreme. We report long-term glycemic control in a patient with PNDM on sulfonylurea therapy, despite initial allergic reaction.

Methods: A Chinese girl presented on the first day of life with persistent hyperglycemia. Despite treatment with various insulin regimens, hemoglobin (Hb) A1c (normal 4.8%–6.3%) increased from 5.0% at 14 days of age to a peak of 9.7% at 15 months of age. Her average insulin dose was 0.5 units/kg/day. Genetic analysis revealed two novel *ABCC8* gene activating mutations encoding the β -cell sulfonylurea-1 receptor of the ATP-sensitive potassium channel. At age 3 years 2 months, transition from insulin to the oral sulfonylurea glyburide was initiated. After 8 days, she developed urticaria, palmar erythema, and a diffuse maculopapular rash, which resolved when medication was discontinued. At age 3 years 11 months, glyburide was reintroduced at a very low dose and was increased with concomitant weaning of insulin over the following 6 months.

Results: Normoglycemia (HbA_{1c} 5.6%) was achieved on glyburide without any further allergic reaction at the age of 4 years 5 months with improved metabolic control. For the next 3 years, HbA_{1c} measurements, and glucose means and variability were significantly lower compared with values during insulin therapy.

Conclusions: As compared with subcutaneous insulin, oral sulfonylureas improved long-term metabolic control in a patient with NDM caused by novel activating mutations in the *ABCC8* gene. Desensitization permitted safe oral sulfonylurea therapy in our patient with NDM despite initial allergic reaction. Fewer episodes of hypoglycemia occurred on sulfonylurea than on insulin therapy, which is an advantage in a very young child.

Keywords: neonatal diabetes; sulfonylurea.

Introduction

Neonatal diabetes mellitus (NDM) is a rare variant of diabetes mellitus with a likely genetic etiology defined by the onset of mild-to-severe hyperglycemia within the first months of life. NDM is rare, occurring in 1 per 300,000–500,000 live births (1). *KCNJ11* and *ABCC8* gene mutations are the major causes of permanent NDM (PNDM). Activating mutations in the *KCNJ11* gene, which encodes the Kir6.2 subunit of the ATP-sensitive potassium channel (KATP) are responsible for between 30% and 64% of all cases of PNDM (2, 3). About 40 mutations in the *ABCC8* gene encoding the β -cell sulfonylurea-1 receptor (SUR1), the regulatory subunit of the KATP channel, have been identified as a cause of PNDM (1, 4–6).

KATP channels of the pancreatic β -cell regulate insulin release. The KATP channel is a hetero-octamer (7–9) assembled from the inward rectifying K-channel Kir6.2 and the high-affinity β -cell SUR1. In the normal pancreatic β -cell, glucose metabolism results in increased intracellular ATP, which binds to Kir6.2 to close the potassium channel, hence depolarizing the membrane and initiating insulin release through increased calcium entry (1, 10, 11). An activating mutation in this channel reduces sensitivity to the inhibitory action of ATP, allowing the potassium channel to remain open. Thus, insulin release is impaired, resulting in hyperglycemia (1, 10).

Case report

Our patient, now 7 years old, was born full term by normal vaginal delivery to Chinese, non-consanguineous parents. Family history of diabetes was negative. She was symmetrically small for gestational age (birth weight 2381 g, length 45.7 cm, head circumference 30 cm; all <5%) but otherwise had a normal physical exam. There was no history of gestational diabetes or perinatal stress.

The patient developed hyperglycemia on the first day of life with blood glucoses (BG) of 141–217 mg/dL. By day 3 of life, she was persistently hyperglycemic with pre-prandial BG 212–236 mg/dL, at which time regular insulin was initiated and titrated to maintain pre-prandial BG of 120–150 mg/dL. At 6 days of life, she was placed on a sliding scale of subcutaneous diluted NPH (1:2) given every 12–24 h. At 13 months, she was transitioned to a pre-prandial sliding scale of NPH (undiluted) and regular insulin, which was changed to glargine plus lispro sliding scale at 18 months. Her mean total daily dose of insulin remained at an average of 0.5 units/kg/day.

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Anti-insulin, anti-islet cell, anti-GAD 65, and thyroid autoimmune antibodies were negative. Work-up for congenital infections, including rubella, was negative. Her initial hemoglobin (Hb) A_{1c} at 14 days of age was 5% (normal <6.3%) and increased to 8.6% at 3 months of age. Her initial C-peptide level on day 6 of life was 0.3 ng/mL (normal 1.1–4.6 ng/mL). Her HbA_{1c} peaked at 9.7% at age 15 months, with highly variable blood glucoses. At 3 years of age, HbA_{1c} was 8.4% (Table 1). Thyroid function tests and lipids were normal.

Genetic analysis

Genetic testing revealed the patient to be a compound heterozygote for novel activating mutations in the *ABCC8* gene for the SUR1 subunit of the pancreatic β -cell sulfonylurea receptor [E1327K, V1523A (in *cis*), and 3127delAC-Cins13 (in *trans*)]. The missense mutation affects residues that are conserved across species and was inherited from her father. The insertion deletion mutation (c.3127_3129delAC-CinsCAGCCAGGACCTG) was inherited from her mother and resulted in a frameshift with premature termination at codon 1116 (T1043QfsX74). Molecular genetic analysis of the *KCNJ11* gene was normal.

Transition to oral sulfonylurea

Following the genetic diagnosis at age 3 years 2 months, the patient underwent an inpatient protocol for transition from subcutaneous insulin to oral sulfonylurea therapy (12). Glyburide therapy was instituted at 0.2 mg/kg/day orally in two daily doses. The dose was increased daily by 0.2 mg/kg/day with concomitant reductions in insulin once fasting BG decreased below 126 mg/dL. By day 7 of this protocol, the glyburide dose was 1 mg/kg/day and the total daily insulin dose decreased to 0.3 units/kg/day from 0.5 units/kg/day upon admission. On day 8 of the protocol, the patient developed urticaria, a diffuse maculopapular pruritic rash, and palmar erythema. Dermatology and Allergy-Immunology services were consulted and advised that the rash was a possible allergic reaction to glyburide, which was subsequently discontinued with rash resolution. The patient was discharged home on her prior insulin regimen with plans to attempt reinstitution of the sulfonylurea at a later date under close supervision.

Desensitization for sulfonylurea

The patient remained on insulin until the age of 3 years 11 months when glyburide was restarted with the consultation of the Allergy-Immunology service using the outpatient protocol reported by Pearson (12). In clinic, 1/100th of the starting glyburide dose was administered with a doubling of the dose every 15 min to a maximum dose of 1.7 mg (0.1 mg/kg/day). No abnormalities in vital signs or physical exam were noted. Glyburide dose increments were made every 1–2 months as an outpatient while the insulin dose was lowered. Adjustments were based on pre-prandial and overnight capillary blood glucose testing results. Within 6 months, the glyburide dose was 1 mg/kg/day divided twice daily and insulin was discontinued, with no further allergic reaction. Subsequently, the glyburide dose was lowered while maintaining excellent glycemic control. At age 7 years, she is on 0.5 mg/kg/day of glyburide. Echocardiogram is normal on glyburide therapy. Her growth continued to follow the 50th percentile for height and for weight.

Improved glycemic control secondary to sulfonylurea therapy

The patient had wide excursions in the blood sugar, including both episodes of hypo- and hyperglycemia, before glyburide therapy (Figure 1). Hypoglycemia occurred less frequently than when on insulin therapy (Figure 1). In fact, after 6 months of glyburide therapy (at 4.4 years old), she achieved euglycemia with an HbA_{1c} 5.6%, mean BG of 123 mg/dL, and C-peptide level of 1.8 ng/mL (normal 0.8–3.1 ng/mL) (Table 1). Since then, she has maintained euglycemia with the most recent HbA_{1c} 5.3%, mean BG of 115 mg/dL, and C-peptide level of 1.06 ng/mL (normal 0.8–3.1 ng/mL) (Table 1), at age 7 years.

Discussion

Insulin is the first-line therapy in all cases of NDM regardless of etiology (1). More recently, oral sulfonylureas, commonly used in adults with type 2 diabetes mellitus, have been used with success in cases of NDM caused by mutations in the *KCNJ11* and *ABCC8* genes (4, 12–18). In the largest published treatment study of patients with NDM

Table 1 Blood glucose control, medication doses, and auxological data before and after glyburide therapy.

Age, years	3.6	3.9	4	4.2	4.4	5	5.2	6	7
Insulin dose, units/kg/day	0.6	0.6	0.5	0	0	0	0	0	0
Glyburide dose, mg/kg/day	0	0.1	0.28	1	0.8	0.57	0.57	0.53	0.5
Hemoglobin A1C, %	8	NA	8.4	6.9	5.6	5.6	NA	5.4	5.3
C-peptide, ng/mL	<0.1	NA	1.4	2.3	1.8	1.2	NA	4.2	1.06
Weight SDS	0.7	0.9	0.89	0.73	0.79	−0.09	−0.41	−0.47	−0.62
Height SDS	−0.19	−0.39	−0.47	−0.38	−0.42	−0.14	−0.24	−0.27	−0.15
BMI SDS	1.3	1.7	1.8	1.6	1.6	0.23	−0.18	−0.48	−0.79

NA, data not available; BG, blood glucose; SDS, standard deviation score. Normal hemoglobin A1c=<6%; normal C-peptide range=1.1–4.6 ng/mL.

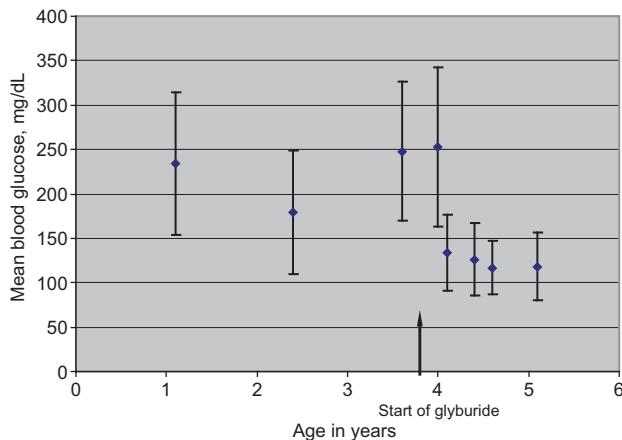


Figure 1 Mean blood glucose (SDS).

due to SUR1 mutations, 85% were successfully transitioned off insulin (4). This study included 27 patients, of which 23 (85%) were successfully treated with sulfonylurea alone. Most had follow-up data for <6 months and only five patients were followed up for 6–13 months. In these five patients, glycemic control continued to improve despite decreasing sulfonylurea doses (4).

Sulfonylureas interact with the KATP channel at two sites: a low-affinity site that lies on Kir6.2 and a high-affinity site located on SUR1 likely accounting for the therapeutic effect, an increase in insulin release (11). Our patient showed an increase in endogenous insulin secretion, evidenced by normal C-peptide levels after sulfonylurea therapy (Table 1), with reduction in both average blood glucose and glucose variability (Figure 1). It is likely that improved insulin sensitivity and β -cell function permitted lowering of her sulfonylurea dose over time. We believe the decreased incidence of hypoglycemia in this young child on sulfonylurea therapy is particularly helpful in an age group where neurological outcomes can be impaired with prolonged or repeated hypoglycemia, and where self-reporting of hypoglycemia does not occur reliably.

Despite the demonstrated cellular effects and clinical success of sulfonylureas in adults with type 2 diabetes mellitus, physicians caring for newborns and children with NDM may hesitate to use sulfonylureas because of potential side effects (4, 12–18), including hypoglycemia, allergic reaction, nausea, vomiting, diarrhea, epigastric fullness, heartburn, and leukopenia. Transitory diarrhea and/or nausea has been noted in a significant number of patients in past medication transfer trials (12, 14, 16). Liver abnormalities, such as cholestatic jaundice, are rare. In the largest treatment trial to date (4), three of 27 patients had side effects on oral sulfonylureas: one had mild transitory diarrhea, one had nausea, and one had severe hypoglycemic requiring a dose reduction. Allergic skin reactions, as seen in our case, can occur but are usually transient. The desensitization protocol we used was successful in avoiding a recurrence of allergic reaction. Of significance, our patient's reaction is the first reported case of skin hypersensitivity in such a medication switch trial.

In addition to reported side effects, the largely unknown interactions of sulfonylureas with extra-pancreatic KATP channels, which also have ABCC8 and KCNJ11 subunits, are of concern for long-term use in children (1). KATP channels are found in cardiac, smooth, and skeletal muscle, adipocytes, and some brain neurons (11). Mutations in ABC transporters have recently been implicated for their roles in cardiac pathology (11, 19). Our patient had persistently normal blood pressure and a normal echocardiogram. There are no studies examining the effect of glyburide on the short- or long-term cardiac health in children.

Use of oral sulfonylurea is less invasive than subcutaneous insulin therapy and therefore preferred by patients and caregivers. We and others have found success in transitioning patients to this method of treatment (4, 12–18). Previous reports showed short-term improved metabolic control with fewer episodes of hypoglycemia. Capillary blood glucose monitoring and close follow-up remains necessary in all patients treated with sulfonylureas. Parents and patients should be cautioned that insulin may be required to control blood sugars during illness (15). The current dose of glyburide in our patient, 0.5 mg/kg/day, is within the range (0.07–2.8 mg/kg/day) found among patients who underwent successful sulfonylurea treatment (4).

In summary, we report a 5-year-old girl with PNDM caused by novel compound heterozygote *ABCC8* gene mutations, who was successfully transitioned to an oral sulfonylurea despite an initial allergic reaction. She remains insulin independent with significantly improved metabolic control, recovery of endogenous insulin secretion, less hypoglycemia, and a decreased glucose excursion rate over a 3-year period. We recommend genetic testing for babies who present with hyperglycemia within the first months of life. Patients with *ABCC8* gene mutations will likely achieve optimal blood sugar control with sulfonylurea therapy. Treated patients should be monitored for known side effects, including hypoglycemia and hypersensitivity reactions. Further research with long-term follow-up in these patients is needed.

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Conflict of interest statement

The authors have no conflict of interest to disclose.

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