

# Case Study: Transitioning From Insulin to Glyburide in Permanent Neonatal Diabetes: Medical and Psychosocial Challenges in an 18-Year-Old Male

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## PRESENTATION

D.R., an 18-year-old man diagnosed with insulin-dependent diabetes as an infant, was identified as an appropriate candidate for genetic testing based on publications identifying a monogenic cause of diabetes in patients diagnosed in the first 6 months of life.<sup>1,2</sup> As a 2.78-kg full-term infant (in the third percentile for weight with intrauterine growth retardation), D.R. initially presented in the Emergency Department at 3 weeks of age with a blood glucose level of 571 mg/dl after 1 week of increased irritability, crying, and decreased oral intake. He was initiated on conventional split-mixed insulin (NPH/regular) twice daily and has been followed ever since by the diabetes team in a large pediatric hospital. Notable history includes moderate developmental delays in reading, writing, and fine and gross motor skills and an identified learning disability in mathematics. Medical history is significant for two presumed hypoglycemic seizures.

At the time of D.R.'s diagnosis, permanent neonatal diabetes mellitus (PNDM) was medically treated as type 1 diabetes. However, in 2004, a specific genetic mutation (KCNJ11 gene) was identified as the cause of neonatal diabetes, and ensuing research confirmed that high doses of oral sulfonylureas are successful in managing neonatal diabetes in selected patients.<sup>1,2</sup> When D.R. was 18 years old, PNDM attributed

to the KCNJ11 R201H (heterozygous) mutation was confirmed by a saliva sample sent for Institutional Review Board–approved research-based analysis at the University of Chicago Diabetes Research and Training Center and follow-up serum analysis performed by the Clinical Laboratory Improvement Amendments–approved University of Chicago Genetics Services Laboratory.

Treatment options were discussed and, after informed consent, D.R. chose a longer outpatient transition rather than completing the transition in an inpatient clinical research unit. Thereafter, the transition from insulin to glyburide was initiated based on the outpatient protocol described by Pearson et al.<sup>2</sup> along with personal communication from Ewan Pearson, MRCP, PhD, and Andrew Hattersley, DM, FRCP, in July 2006 and June 2007, respectively, and modifications by Louis Philipson, MD, PhD, in July 2006.

These personal communications provided additional information to assist in the transition from insulin to glyburide in an outpatient setting. Specific instructions in terms of the choice of sulfonylurea (glyburide) and typical range of glyburide required (0.13–1.2 mg/kg body weight/day) with the possibility of amounts up to 1.5 mg/kg/day were recommended. An outpatient schedule documenting glyburide

incremental increases with associated insulin tapering was also provided. Adverse gastrointestinal, hematological, dermatological, and hepatic reactions were noted to be possible based on adult experience with glyburide. Thus, close monitoring of complete blood counts and liver and renal function tests was recommended in addition to seeing the patient weekly with phone accessibility during the transfer.

The treatment team immediately recognized that significant anxiety developed during the transition and, therefore, instructed D.R. to keep a daily journal. As both the transition and anxiety progressed, a psychology team consultation was requested to address the significant lifestyle modifications necessary for D.R.'s new diabetes regimen.

Glyburide was initiated at 0.1 mg/kg/day and increased to 1 mg/kg/day by week 8. Concurrently, insulin was decreased weekly by 25% until discontinuation at week 8 (Table 1). At week 12, because of hyperglycemia secondary to decreased exercise and increased carbohydrate intake, basal insulin glargine was added to the daily regimen. By week 21, glyburide dosing was 1.39 mg/kg/day divided into three doses per day, and glargine was discontinued. As an adjunct to the Pearson protocol, sitagliptin, 100 mg/day, was added at week 22 to facilitate endogenous insulin

**Table 1. Overview of the Transition From Insulin to Glyburide**

Week	Glyburide (mg) Morning/3:00 p.m./Night	Insulin (units)	A1C (%)	Average Blood Glucose (mg/dl)				C-Peptide (ng/ml)	Medical/Psychological Intervention
				B	L	D	HS		
Week 1	3.75/—/3.75 (0.11 mg/kg/day)	15 N/15 R AM 15 N/15 R PM (0.93 units/kg/day)	9.4	253	—	265	239	<0.05	Transition initiated. D.R. asked to keep journal.
Week 3	12.5/—/12.5 (0.4 mg/kg/day)	12 N/11 R AM 12 N/8 R PM (0.71 units/kg/day)		140	159	140	182	0.07	D.R. reported side effects (diarrhea, increased sensitivity to low blood glucose levels, weight loss, difficulty with intense exertion in sports).
Week 5	25/—/25 (0.8 mg/kg/day)	8 N/8 R AM 10 N/6 R PM (0.47 units/kg/day)		138	244	146	164	1.3	D.R.'s journal revealed themes of anxiety, lack of improvement in quality of life: "I'm still waiting for this to 'make my life so much better.'"
Week 7	25/—/25 (0.8 mg/kg/day)	3 N/3 R AM 3 N/2 R PM (0.17 units/kg/day)		170	263	154	191	1.6	Discontinuation of insulin. Journal revealed resistance to change: "If I had known it would be like this, I never would have agreed to go through with it."
Week 9	30/—/30 (0.98 mg/kg/day)	None	8.7	172	333	183	334	2.8	Elevated blood glucose levels with discontinuation of insulin. Glyburide three times daily; glargine initiated at week 10.
Week 12	30/30/10 (1.15 mg/kg/day)	10 G AM		113	130	145	226	2.4	Psychology session scheduled to address anxiety, resistance to change, and loss of autonomy. D.R. encouraged to take active role in transition. D.R. selected one goal (drink low-carb shake).
Week 17	30/30/10 (1.15 mg/kg/day)	6 G AM		129	71	164	213	3.1	GAD antibodies elevated (6.32 IE/ml); normal: 0.00–1.45 IE/ml); sample sent to international laboratory to determine HLA typing.
Week 20	20/40/10 (1.15 mg/kg/day)	6 G AM	8.1	85	81	148	264	3.2	Glargine discontinued. Glyburide increased to 1.39 mg/kg/day.
Week 21	25/45/15 (1.39 mg/kg/day)	None		105	n/a	182	311	3.9	Results from research laboratory: HLA genotype: DQB1*0502/0504-DQB1*0606. "Neutral"—"non-high-risk" for type 1 diabetes.
Week 22	30/50/10 (1.45 mg/kg/day)	None		91	n/a	160	266	2.9	Moved dinner time dosing of glyburide to 3:00 p.m. Initiated sitagliptin, 100 mg AM.
Week 23	30/50/10 (1.49 mg/kg/day)	Sitagliptin 100 mg AM		107	n/a	101	203	3.6	Initiated 3-day trial of CGM to provide additional information about trends in blood glucose levels.

Table 1. Overview of the Transition From Insulin to Glyburide, continued

Week	Glyburide (mg) Morning/3:00 p.m./Night	Insulin (units)	A1C (%)	Average Blood Glucose (mg/dl)				C-Peptide (ng/ml)	Medical/Psychological Intervention
				B	L	D	HS		
Week 24	30/50/10 (1.49 mg/kg/day)	Sitagliptin 100 mg AM		133	n/a	158	209	3.6	CGM results led to change in glyburide dosing: 30 mg AM; 30 mg at 3:00 p.m.; 30 mg PM.
Week 45	22.5/30/30 (1.35 mg/kg/day)	Sitagliptin 100 mg AM	7.1	84	n/a	89	161	3.4	Decreased 3:00 p.m. dose of glyburide to 27.5 mg to address low blood glucose levels at dinner.
Week 55	20/22.5/20 (1.02 mg/kg/day)	None	6.6	107	175	123	185	2.6	Sitagliptin discontinued at week 52. D.R. reports eating "whatever he wants" without monitoring carbohydrates. D.R. reports satisfaction with current regimen.

AM, morning; B, breakfast; L, lunch; D, dinner; G, glargine insulin; HS, bedtime; N, NPH insulin; PM, nighttime; R, regular insulin.

production and address continued occasional hyperglycemia.

Continuous glucose monitoring (CGM) for a 72-hour period revealed a consistent rise in blood glucose levels from 3 hours after dinner until 4:00 a.m. Blood glucose levels then decreased steadily until 10:00 a.m. (upon awakening), reminiscent of typical patterns in type 2 diabetes.<sup>3</sup> This crucial information obtained from CGM data resulted in improved timing and dosing of the glyburide.

During the initial stages of the transition, D.R. experienced weight loss (3.8 kg in 3 weeks), mild diarrhea, occasional abdominal pain, and a mild transient elevation of liver transaminases; there were no noted increases in alkaline phosphatase or bilirubin levels. All side effects were temporary.

At 55 weeks, D.R.'s regimen was stabilized at glyburide, 1.02 mg/kg/day, divided into doses of 20 mg every morning, 22.5 mg at 3:00 p.m., and 20 mg every night. His metabolic control was significantly improved, as evidenced by 14-day blood glucose levels averaging 147.5 mg/dl, and A1C of 6.6%, and a random C-peptide level of 2.6 ng/ml (normal range: 1.3–7.9 ng/ml). D.R. also reported a relative improvement in his gross motor skills, with his competitive running race times improving throughout the transition. Table 1 provides complete medical information.

**QUESTIONS**

1. What are the unique challenges of diagnosing PNDM and initiating transition from injected insulin to glyburide in a young adult?
2. What are the practical implications of performing the transition to oral sulfonylureas in an outpatient?
3. What are the medical and psychosocial barriers that may prevent

a successful transition to a new diabetes care regimen that is perceived to be superior?

**COMMENTARY**

PNDM usually presents in the first 6 months of life and, until recently, was treated with the conventional insulin regimens associated with type 1 diabetes. However, after several investigators noted an absence of autoimmune markers in select patients with PNDM,<sup>4</sup> mutations in the kir6.2 subunit (encoded by KCNJ11) of the K<sup>ATP</sup> channel of the pancreatic β-cell were identified as an important cause of PNDM, followed by additional mutations in the other K<sup>ATP</sup> subunits encoded by the ABCC8 gene.<sup>1</sup>

Transitions from injected insulin to relatively high doses of oral sulfonylureas (0.8–1.8 mg/kg body weight/day) have successfully eliminated the insulin requirement in infants, young children, and adults identified as positive for the KCNJ11 mutation.<sup>2,5,6</sup> Furthermore, families typically note improved quality of life<sup>5,6</sup> resulting from the transition to oral sulfonylureas. However, the process from diagnosis of PNDM to the completion of the outpatient transition to a glyburide-based regimen has not been addressed for a young adult.

With all novel treatments, particularly when a protocol is newly established, flexibility is necessary to define what works best for each individual. In contrast to rapid transitions typically employed in inpatient protocols,<sup>5–7</sup> outpatient protocols use a gradual approach to discontinuing insulin and initiating glyburide. Despite clear steps delineated in the outpatient protocol recommended by Pearson et al.,<sup>2</sup> factors such as timing and distribution of glyburide are not specifically defined, nor has there been careful consideration of carbohydrate intake

and exercise and how these factors affect blood glucose levels.

In this case, because it was hypothesized that glyburide-treated PNDM was similar to mild type 2 diabetes, sitagliptin, a relatively new adjunct to type 2 diabetes in adults, was added to the glyburide protocol.<sup>8</sup> Sitagliptin, a dipeptidyl peptidase IV (DPP-IV) inhibitor has been shown to lower blood glucose levels through enhancement of glucose-stimulated insulin secretion in patients with type 2 diabetes. Furthermore, Pearson et al.<sup>2</sup> demonstrated that use of sulfonylureas resulted in an improved insulin secretory response of the  $\beta$ -cell but did not increase incretin secretion. Rather, there was an improved response of the  $\beta$ -cell to incretins.<sup>2</sup> Therefore, it was anticipated that DPP-IV inhibition could stimulate the release of insulin, inhibit the release of glucagon, and improve further glucose homeostasis<sup>9</sup> in patients with PNDM. Indeed, as noted in Table 1, random concentrations of the C-peptide of proinsulin (a marker for endogenous insulin secretion) increased significantly after the initiation of sitagliptin. And because sitagliptin may be given orally, it was an addition our patient found acceptable. It is important to note, however, that DPP-IV inhibitors do not yet carry an official Food and Drug Administration indication for treatment of PNDM.

This case also demonstrated that employing CGM as a diagnostic tool can assist in the distribution and timing of glyburide and provide critical information about blood glucose variability throughout the course of the day.

In addition, this case contributes to the growing body of knowledge about learning difficulties associated with PNDM. D.R.'s history of learning and motor delays is similar to those reported in other PNDM

patients with the KCNJ11 R201C and R201H mutations<sup>7</sup> but was less severe than the V59M mutation associated with developmental delay and speech and motor disorders.<sup>10</sup>

With sulfonylurea treatment, there is some evidence to suggest that D.R.'s gross motor skills improved, as evidenced by his faster race times. Although his mild motor impairments may also have been related to early experiences of hypoglycemic or hyperglycemic episodes, recent case reports have demonstrated notable motor improvement in toddlers with PNDM and V59M mutation after initiation of oral sulfonylureas.<sup>11</sup> This associated finding of improved race times highlights the need for further research in PNDM and related impairments, including presentation of case reports and inclusion of all patients diagnosed with PNDM in longitudinal databases, such as the Neonatal Diabetes Registry ([www.neonatal-diabetesregistry.org](http://www.neonatal-diabetesregistry.org)).

To our knowledge, this is the first case report that discusses the psychosocial barriers to implementing oral treatment of PNDM. Because our patient was a young adult, the transition's success was heavily dependent on his agreement to, and cooperation with, the established protocol. The differing perceptions in quality of life among D.R. and the treatment team are particularly noteworthy. D.R. was initially resistant to changing daily self-care routines; thus, what his medical team assumed to be an improvement in quality of life (by replacing injections with oral medications) was not necessarily perceived as true by the patient. In fact, D.R. noted that he was "merely trading one dependency for another." The increased medical and parental attention to diabetes management and frequent clinic visits associated with this transition were

also viewed as significant intrusions and threats to his autonomy.

D.R. also expressed significant difficulty altering behaviors and cognitions that had guided his diabetes management for the past 17 years. Taking less insulin was in direct conflict with his perception of diabetes management, and he feared deterioration in metabolic control. Coordinated care with diabetes team psychology services enhanced patient-centered communication and treatment. The use of a patient journal coupled with motivational interviewing techniques allowed D.R.'s concerns to be openly addressed by the treatment team. Acknowledgment of these psychosocial barriers and patient-directed goal setting allowed for D.R. to be an active participant in the transition and increased overall adherence to the treatment regimen.

Because most patients have been transitioned rapidly in an inpatient clinical research unit, our outpatient experience has significant implications for future neonatal diabetes patients identified with  $K^{ATP}$  mutations and also provides fascinating insights into the complex psychology of intensive diabetes management. The use of a multidisciplinary diabetes team enhanced our ability to identify salient challenges and proceed with the treatment regimen. As an increasing number of adolescent and adult patients initiate the transition to oral sulfonylureas, attention should be paid to the critical, but often overlooked, psychological factors associated with such a monumental shift in treatment. Individualized clinical care goals should be set with each patient and family to ensure successful outcomes.

#### CLINICAL PEARLS

- Transition to a new, presumably superior, medical regimen

proven effective by evidence-based medicine is not necessarily easily accomplished in practice.

- Outpatient transition to glyburide in a patient with the KCNJ11 mutation results in different challenges than those observed during the inpatient transition process.
- Distribution of medication may be assisted by current technology such as CGM.
- Use of a longitudinal database, such as Neonatal Diabetes Registry, should be encouraged for all practitioners working with patients diagnosed with PNDM and can help identify additional benefits of and barriers to treatment with oral sulfonylureas.
- The psychosocial team may play an important role in helping young adults who are accustomed to managing presumed type 1 diabetes adjust to a newly diagnosed disease process with resultant changes in therapy.

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