Transfer to Sulphonylurea Therapy in Adult Subjects With Permanent Neonatal Diabetes Due to *KCNJ11*-Activating Mutations

Evidence for improvement in insulin sensitivity

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Activating mutations in the *KCJN11* gene encoding in the ATP-sensitive K^+ channel (K_{ATP} channel) subunit Kir6.2 were reported (1) as the most common cause of permanent neonatal diabetes (PND). Recently, it has been shown that most subjects with Kir6.2 mutations could be switched from insulin to sulfonylurea and that such treatment is both safe and highly effective, at least in the short term (2,3). Notably, the majority of reported successfully transferred patients were children. Data on adults are very scarce, and there are few mutation carriers transferred off insulin (2,4). Moreover, some adult subjects are unable to switch from insulin to sulfonylurea (2).

We have recently identified four adult carriers of a Kir6.2 mutation and provided evidence that they, before the sulfonylurea exposure, were characterized by decreased insulin sensitivity (5). Here, we report their successful transfer to sulfonylurea.

RESEARCH DESIGN AND METHODS — To dissect the genetic background of PND in Poland, the Nationwide Registry has recently been established. Four adult subjects with Kir6.2-activating mutations were identified by the end of 2005. Three subjects carried the R210H mutation, while one individual had the K170N substitution. They were included in the current project, which aimed to switch from insulin to sulfonylurea and to assess, by hyperinsulinemic-euglycemic clamp, whether the alteration in insulin action occurs after this transfer. The study protocol and informed-consent procedures were approved by the ethics committee of Jagiellonian University. The project was conducted according to the rules of the Declaration of Helsinki.

RESULTS — To rapidly switch treatment, three women (Pol13, -14, and -17, respectively) were hospitalized at the Department of Metabolic Diseases, Jagiellonian University Medical College, Krakow, Poland, for the transfer and treatment by glipizide gastrointestinal therapeutic system was initiated. Pol13 and -14, both R201H mutation carriers, became completely insulin independent within 14 days. Both initially required 50 mg glipizide. For Pol17 (K170N mutation), the fast transfer was initially unsuccessful and she was released from the hospital on a combined treatment of 60 mg glipizide gastrointestinal therapeutic system and 25 units insulin. After 2 months of observation, glipizide was replaced with 60 mg glibenclamide and insulin continued. Over the subsequent weeks, the requirement for insulin in Pol17 decreased, and she became fully insulin independent after 4 months from the initial exposure to sulfonylurea. In Pol19, a 50-year-old man with R201H mutation, a slower outpatient protocol was used. This patient was able to stop insulin treatment at the final daily glipizide dose of 45 mg. We confirmed the effectiveness of his sulfonylurea therapy by using a continuous glucose monitoring system.

Transitory nausea was reported in the first few days of treatment by all patients. No other side effects were observed. The average age of the transferred patients was 31.5 years (range 20–50). Pol19 was probably the oldest reported Kir6.2-mutation carrier transferred to sulfonylurea. After 1 month of excellent metabolic control, this patient, however, requested to return to insulin therapy for socioeconomic reasons.

Six months after the initiation of sulfonylurea therapy, Pol13, -14, and -17 were available for the follow-up. In Table 1, we summarized their clinical data. At that time, Pol13 and -14 were completely free of insulin for 6 months and Pol17 for 2 months. We saw improvement in metabolic control in all three cases as measured by A1C, accompanied by sulfonylurea dose reduction. No major episode of hypoglycemia was reported. Surprisingly, weight loss was observed in all three patients. On average, subjects lost 7.8 kg, with the largest decrease occurring in Pol14 (12.9 kg); Pol17 lost the least amount of weight (3.7 kg). Despite low BMI, these women did not report any abnormalities in menstrual cycle.

Before the hyperinsulinemic-euglycemic clamp, patients received the usual sulfonylurea dose; otherwise,

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Abbreviations: K_{ATP} channel, ATP-sensitive K^+ channel; PND, permanent neonatal diabetes.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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Table 1—*Clinical characteristics of adult patients with PND due to Kir6.2 mutations*

	Pol13	Pol14	Pol17	Pol19
Sex	F	F	F	M
Mutation	R201H	R201H	K170N	R201H
Birth weight (g)	Unknown	2,600	2,200	3,200
Age diabetes diagnosed (months)	2	3	2	3
Age at examination (years)	34	20	22	50
Height (cm)	150	160	168	168
Weight (kg)				
At study entry	51.1	58.0	51.8	62.2
At follow-up	44.2	45.1	48.1	NA
BMI (kg/m^2)				
At study entry	22.7	22.7	18.4	22.0
At follow-up	19.6	17.6	17.0	NA
Daily insulin dose at study entry (units)	58	40–45	55	23
Sulphonylurea used	Glipizide gastrointestinal therapeutic system	Glipizide gastrointestinal therapeutic system	Glibenclamide	Glipizide gastrointestinal therapeutic system
Initial sulphonylurea dose (mg)	50	50	60	45
Sulphonylurea dose at follow-up (mg)	40	30	50	NA
Serum creatinine level at study entry (μmol/l)	68.4	58.5	64.6	84.8
A1C (%)				
At study entry	7.2	8.7	10.2	9.7
At the end of follow-up	5.9	5.3	7.8	NA
Serum fasting C-peptide level (ng/ml)				
At study entry	0.18	0.10	<0.05	<0.05
After transfer	1.88	1.06	1.71	NA
Insulin sensitivity (mg · kg^{-1} · min^{-1})				
M at study entry	3.91	2.76	6.66	4.64
M at follow-up	13.40	7.06	10.50	NA
Total cholesterol level (mmol/l)				
At study entry	3.1	4.3	6.7	4.8
After transfer	3.2	2.9	5.0	NA
Triglyceride level (mmol/l)				
At study entry	0.75	0.74	1.27	1.40
After transfer	0.79	0.75	1.51	NA
Retinopathy				
At study entry	Proliferative DR; prior multiple laser coagulations	Nonproliferative DR	Nonproliferative DR	No DR
At follow-up	Progression; required additional lasers	Regression	Regression	NA
Albumin/creatinine ratio (mg/mmol)				
At study entry	11.4	0.5	0.4	Not examined
At follow-up	2.8	0.8	1.0	NA

DR, diabetic retinopathy; NA, not applicable.

protocol was as previously described (5). A substantial improvement in insulin sensitivity was seen in all examined patients (mean M index increase 5.88 mg · kg^{-1} · min^{-1} [range 3.84–9.49]). With this very limited sample size, the differences of M indexes before and after sulfonylurea therapy in the paired *t* test reached only borderline significance ($P = 0.08$).

CONCLUSIONS — Here, we have reported new, important observations on PND due to Kir6.2 mutations. First, the successful transfer off insulin to sulfonylurea is feasible in adults, and age should

not be considered the contraindication for such a transfer. Some patients, however, may require up to several months of exposure to large sulfonylurea doses before they become fully insulin independent. Second, a decrease in body weight was seen in our patients despite being generally encouraged to continue the previous isocaloric diet and to maintain the initial body weight. One may try to explain this by the cessation of insulin therapy. On the other hand, sulfonylurea action in Kir.6.2-mutation carriers in endocrine pancreas seems to be largely mediated by incretins (2). Since the activation of incretin axis is associated with the anorectic effect (8), it is possible to hypothesize that higher-than-usual therapeutically used doses of nonselective sulfonylurea may also enhance this phenomenon. Additionally, one cannot entirely exclude that high doses of extended-release formulation of glipizide tablets could have influenced the study outcome. Two larger recently published studies (2,3) did not report weight reduction; however, they included either an entirely or predominantly pediatric population and mostly used glibenclamide. Further observation will determine whether the weight loss seen in our patients has permanent or transient nature. A third observation is an increase in insulin sensitivity after the transfer. The reduction in glucotoxicity, as previously described (4) in type 1 diabetes, and weight loss constitute the possible reasons. However, the magnitude of this improvement allows us to examine other causes; in other study groups either much smaller effects (9) or even no influence (10) of weight loss on insulin-stimulated glucose disposal were seen as assessed by hyperinsulinemic-euglycemic clamp. An explanation may be offered by a putative direct influence of sulfonylurea on muscular K_{ATP} channels. In an animal model, the Kir6.2 knockout mice had increased insulin sensitivity (6), which is in line with activating mutations of *KCNJ11* having an opposite effect in humans (5). Closure of K_{ATP} channels in muscles by high doses of sulfonylurea could make the patients more insulin sensitive and facilitate the transfer. We also observed clinical heterogeneity among our patients; for example, Pol17 lost the least amount of weight and gained the least insulin sensitivity. There are several possible explanations of this phenomenon, such as a different type of mutation, variability in polygenic background, and possibly even the type of sulfonylurea used for the transfer. Finally, our observations are based, as seen frequently in monogenic diabetes, on just a few cases and thus they warrant further confirmation.

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