Sulfonylurea treatment outweighs insulin therapy in short-term metabolic control of patients with permanent neonatal diabetes mellitus due to activating mutations of the *KCNJ11* (*KIR6.2*) gene

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To the Editor,

Activating missense mutations in the gene encoding potassium inwardly rectifying channel, subfamily J, member 11 (*KCNJ11*) represent the most common cause (40 to 64%, depending on populations) of permanent neonatal diabetes mellitus in patients diagnosed in the first 6 months of life [1, 2]. In addition, *KCNJ11* activating mutations can lead to transient/relapsing neonatal diabetes [3, 4]. The *KCNJ11* gene encodes the pore-forming subunit (also known as *KIR6.2*) of the pancreatic beta cell ATP-sensitive potassium channel (K_{ATP}), which exerts a pivotal role in

glucose-regulated insulin release. In the beta cell, *KIR6.2* forms a hetero-octameric complex (4:4) with the sulfonylurea receptor subtype 1 (*SUR1*); binding to *SUR1* by sulfonylureas determines channel closure and insulin secretion [2].

In previously published cases, seven patients have been reported to respond well to the transfer from insulin to oral hypoglycaemic agents [4–8]. Here we report on the replacement of insulin with sulfonylureas in ten Italian children who have mutations in *KCNJ11* (R50P, V59M [x4], K170R, R201C and R201H [x3]) and were followed in nine

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different centres for paediatric diabetes. Mutation detection in six of these patients has been previously reported [9]. The newly identified patients, known here by patient numbers nd-CH/1 (R201H), nd-MI/1 (V59M), nd-NA/9 (R201H) and nd-TN/1 (R201H), did not show any peculiar clinical feature. Birthweight was low for gestational age in patients nd-CH/1, nd-NA/9 and nd-MI/1 (2,100 g/41 weeks/<first centile; 1,840 g/35 weeks/third centile; 2,740 g/40 weeks/tenth centile, respectively), who presented with diabetes at 41, 61 and 92 days of life. In patient nd-TN/1 birthweight was normal (3,130 g/40 w) with diabetes onset at 104 days from birth. Patient nd-MI/1 (V59M) also had a severe delay in motor and mental development, as well as epilepsy. In addition, autism was diagnosed in this patient at 4 years of age, after exclusion of other causes leading to behavioural disorders. Parents of patients nd-CH/1, nd-MI/1, nd-NA/9 and nd-TN/1 had wild-type sequence at the *KCNJ11* locus, thus mutations arose de novo in all patients.

Glibenclamide was used in eight probands (6 below 30 months of age at the time of transfer), while the remaining two were treated with glipizide as out-patients. In those too young to swallow tablets, a commercial brand of glibenclamide was ground to a fine powder, re-suspended in water at a concentration of 5 mg/ml (or 0.25 mg/drop) and administered as solution. After admittance to the local paediatric diabetes ward, glibenclamide was introduced at a starting dose of between 0.07 and 0.68 mg kg⁻¹ day⁻¹. Various scale-up schemes were used, with dose increments performed every day or every other day, and gradual insulin withdrawal. In these eight patients, insulin was completely stopped within 3 to 12 days. Good metabolic control (i.e. postprandial blood glucose concentrations below 11.1 mmol/l) was attained in all cases using three daily administrations synchronised with the main meals and with final doses of between 0.16 and 0.8 mg kg⁻¹ day⁻¹ (Table 1). After discharge from the hospital, the amount of glibenclamide was reduced in seven patients with decrements of 10 to 73% of the initial dose (dose range at home: 0.18–0.57 mg kg⁻¹ day⁻¹). Dose reduction at home was performed according to the results of frequent glucose monitoring by the parents, who had been instructed with a view to achieving strict metabolic control. There were no episodes of hypoglycaemia during hospitalisation or at home. Two cases (nd-PR/1, nd-BA/1) were treated with glipizide as out-patients, with a starting dose of 0.2 mg kg⁻¹ day⁻¹ and increments every 14 to 30 days. Patient nd-BA/1 (V59M) was weaned off insulin in 42 days at a sulfonylurea dose of 0.55 mg kg⁻¹ day⁻¹, while the parents of patient nd-PR/1 completely stopped insulin after 13 months of sulfonylurea treatment at a dose of 0.61 mg kg⁻¹ day⁻¹ (Table 1). No side effects or adverse reactions to sulfonylurea were seen at any dosage, but single-day episodes of diarrhoea occurred in two patients at peak dosage.

Individual insulin needs at the time of switching to the oral drug and final glibenclamide/glipizide dose were variable (Table 1) with no evident relationship with mutation type or age. Fasting C-peptide, as assayed in each local hospital, was only detectable in patients nd-CH/1, nd-TN/1 (Table 1) and became measurable in all patients during sulfonylurea treatment (Table 1). HbA_{1c} values (local assay) available in all cases after at least 2 months of sulfonylurea therapy (mean: 9 months) indicated surprisingly good metabolic control (mean: 5.9%; range: 4.9–7.4%), with a mean decrease of 2% (and up to 4.6% in a single patient). However, no improvement of the neurological manifestations was recorded in patient nd-MI/1 while on sulfonylurea therapy.

Establishing an effective chronic insulin treatment in newborns and infants with diabetes is certainly a challenge for the clinician and even more for the patients' parents. Insulin injections themselves and intensive glucose monitoring at home in order to prevent and/or to treat hypoglycaemic episodes carry a high psychological burden for the parents. The discovery that activating mutations of *KCNJ11* causing permanent or transient neonatal diabetes can respond to sulfonylureas [1, 2, 4–8] opened the possibility of treating patients who have this genetic defect with oral hypoglycaemic agents. In previous studies [4, 9], this report and in unpublished observations (F. Barbetti), the Italian Study Group of Early-Onset Diabetes has identified 16 unrelated subjects with eight different *KCNJ11* mutations. To date, one subject with *KCNJ11*-related transient/relapsing neonatal diabetes [4] and ten patients from the Italian cohort of *KCNJ11*-related permanent neonatal diabetes mellitus have been successfully transferred from insulin to sulfonylurea. In regard to the five patients still receiving insulin therapy, three were only recently diagnosed, whilst the parents of the other two refused the sulfonylurea trial.

Cases with various *KCNJ11* mutations (V59M, R201H [x 4], R201L, V333I) [1, 2, 4–8] who were transferred to glibenclamide or other sulfonylureas have been previously published as single-case reports [2, 6–8], or as small-group (three patients) reports [5]. Our experience is valuable for at least three aspects. Firstly, we clearly show in a sizeable number of patients that sulfonylurea treatment is invariably superior to insulin in short-term metabolic control. Secondly, we demonstrate that the newly described R50P and K170R mutations [9] are also sensitive to the effects of sulfonylurea. Thirdly, we report that patients with the mutation V59M attained good metabolic control at a low–medium glibenclamide dose (0.18–0.5 mg kg⁻¹ day⁻¹), not higher than that used in patients with the R201H mutation (0.16–0.47 mg kg⁻¹ day⁻¹).

Our result is comparable to that obtained in another patient who has permanent neonatal diabetes mellitus and

Table 1 Response to sulfonylurea treatment in patients with permanent neonatal diabetes due to KCNJ11 mutations

Patient	Mutation	E23K polym. genot	Insulin dose (U kg ⁻¹ day ⁻¹)	Age at switch to SU	SU dose (mg kg ⁻¹ day ⁻¹) at discharge and (→) at home	Fasting C-peptide (nmol/l) before transfer to SU	Fasting C-peptide (nmol/l) while on SU	HbA _{1c} while on insulin	HbA _{1c} while on SU	Duration of SU therapy
nd-TO/2	R50P	EE	0.71	10 years	0.80→0.57	Not detectable	0.23	7.2	6.3	10 months
nd-NA/5	V59M	EK	0.6	17 months	1.1→0.5	Not detectable	0.2	9.8	5.2	7 months
nd-TS/1	V59M	EK	0.9	28 months	0.7→0.39	Not detectable	0.3	9.2	5.8	14 months
nd-MI/1	V59M	EK	0.92	9 years	0.66→0.18	Not detectable	0.39	8.0	5.4	1 year
nd-RM/1	R201C	EK	0.3	22 months	0.75→0.32	Not detectable	0.12	7.3	6.7	1 year
nd-CH/1	R201H	EK	0.92	6 months	0.76→0.47	0.1	0.2	6.4	5.4	2 months
nd-NA/9	R201H	EK	0.48	7 months	0.41→0.37	Not detectable	0.2	7.9	4.9	4 months
nd-TN/1	R201H	EK	0.55	23 months	0.16	0.26–0.53	0.7	7.1	5.5	2 months
nd-BA/1	V59M	EK	0.6	9 years	0.55 ^b	Not detectable	0.06	7.7	5.8	6 months
nd-PR/1	K170R ^a	EK	0.7	8 years	0.61 ^b	Not detectable	0.21	8.4	7.4	14 months

SU Sulfonylurea

^aPatient nd-PR/1 also carries the heterozygous glucokinase inactivating (i.e. MODY2) mutation G44S^bIndicates that glipizide instead of glibenclamide was used in these patients

carries the V59M mutation; this patient was weaned from insulin at a dose of glibenclamide of $0.3 \text{ mg kg}^{-1} \text{ day}^{-1}$ [5], lower than the doses used in the two patients with the R201H mutation, as reported in the literature (0.4 and $0.8 \text{ mg kg}^{-1} \text{ day}^{-1}$) [5, 6]. These data are in keeping with experimental data showing that mutation V59M is at least as sensitive to glibenclamide as the transient neonatal diabetes-related KCNJ11 mutation I182V [10].

In summary, we believe that sulfonylurea therapy is feasible in most patients with KCNJ11-related permanent neonatal diabetes mellitus.

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