Fetal Macrosomia and Neonatal Hyperinsulinemic Hypoglycemia Associated With Transplacental Transfer of Sulfonylurea in a Mother With KCNJ11-Related Neonatal Diabetes

Objective
Sulfonylureas (SUs) are effective at controlling glycemia in permanent neonatal diabetes mellitus (PNDM) caused by KCNJ11 (Kir6.2) mutations.

Research Design and Methods
We report the case of a woman with PNDM who continued high doses of glibenclamide (85 mg/day) during her pregnancy. The baby was born preterm, and presented with macrosomia and severe hyperinsulinemic hypoglycemia requiring high-rate intravenous glucose infusion.

Results
Postnatal genetic testing excluded a KCNJ11 mutation in the baby. Glibenclamide was detected in both the baby’s blood and the maternal milk.

Conclusions
We hypothesize that high doses of glibenclamide in the mother led to transplacental passage of the drug and overstimulation of fetal β-cells, which resulted in severe hyperinsulinemic hypoglycemia in the neonate (who did not carry the mutation) and contributed to fetal macrosomia. We suggest that glibenclamide (and other SUs) should be avoided in mothers with PNDM if the baby does not carry the mutation or if prenatal screening has not been performed, while glibenclamide may be beneficial when the fetus is a PNDM carrier.
PNDM, the high SU doses used are of concern. Two case reports (8,9) on SU use in women with PNDM during pregnancy (three pregnancies) have been published. We report the case of a woman with PNDM due to KCNJ11 mutation where the continuation of high doses of SUs in pregnancy led to transplacental transfer, which resulted in prolonged neonatal hyperinsulinemic hypoglycemia and contributed to fetal macrosomia.

RESEARCH DESIGN AND METHODS
Genetic testing for neonatal diabetes was performed by the Department of Molecular Genetics, Royal Devon & Exeter Hospital, Exeter, U.K.

Glibenclamide levels in serum and breast milk were measured with a very sensitive and reproducible liquid chromatography-tandem mass spectrometry assay. Calibration standards were prepared in blank serum at the following concentrations (in ng/mL): 1,000, 500, 200, 100, 50, 20, 5, 1, and no drug. D11-glibenclamide was added at 333 ng/mL as an internal standard, and standard samples as well as unknowns were processed in triplicate and within the same batch. Sample aliquots (60 μL) were processed by acidification with 4% orthophosphoric acid (60 μL) and C18 reverse-phase–solid-phase extraction, and analysis by liquid chromatography-mass spectrometry on an ion trap mass spectrometer (AmaZon; Bruker Daltonics) using pseudo-selected reaction monitoring acquisition with monitoring of mass transitions 494.1 → 369.0 and 505.1 → 369.0 for glibenclamide and d11-glibenclamide, respectively. Blank human breast milk was donated by a volunteer and was used to prepare calibration standards with the following concentrations (in ng/mL): 150, 100, 50, 30, 15, 5, 1, and no drug. Sample preparation was carried out using a modified extraction protocol suitable for human milk samples (10). The lower limit of quantification (defined by <20% deviation from theoretical values) in both serum and breast milk determinations was 5.0 ng/mL.

RESULTS
A 30-year-old G2 P1 Caucasian woman with KCNJ11-related neonatal monogenic diabetes presented at 6 weeks into her second pregnancy. The mother herself had received a diagnosis of neonatal diabetes at 3 months of age and had been treated exclusively with insulin (based on the assumption that she had type 1 diabetes) until a genetic diagnosis was made after her first child was born. She was treated with an insulin pump in preparation for and during her first pregnancy. Metabolic control was perfect with an HbA1c level of 5.4% (36 mmol/mol). The first baby girl was born vaginally at 38 weeks and was small for her gestational age (weight 2,180 g [<3rd percentile], length 48 cm [25th percentile]). Her neonatal glucose levels were normal without any hypoglycemia. At the age of 3 months, the baby was admitted to the hospital with diabetic ketoacidosis. Insulin pump therapy was started, and genetic testing was performed. The diagnosis of PNDM was confirmed: the patient had a heterozygous missense mutation (p.G334C) in the KCNJ11 gene, and the same mutation was subsequently documented in her mother. Both child and mother were switched from insulin to SU therapy and achieved excellent glycemic control.

The second pregnancy was initiated under SU therapy (glibenclamide 85 mg/day, weight 52 kg [prepregnancy weight]), as the literature suggested that continuing SU therapy during pregnancy in a patient with PNDM should be safe (8,9). This is a high dose of SU, even for nonpregnant patients. Maternal glycemic control during pregnancy was good (mean HbA1c level 6.1% [43 mmol/mol], starting HbA1c level 6.1% [43 mmol/mol], HbA1c level at delivery 6.4% [46 mmol/mol]). Doses of glibenclamide were increased to 90 mg/day on the basis of self-monitored glycemia. The mother went into preterm labor at 36 weeks’ gestational age, which was reversed by administration of tocolyzsin and nifedipine; in addition, antenatal betamethasone was given. The baby was delivered at 33 weeks and 3 days by cesarean section because of ongoing labor and known macrosomia: birth weight was 3,600 g (>97th percentile), and length was 50 cm (97th percentile). Hypoglycemia developed in the baby boy (first measured value was 16 mg/dL), and he required high doses of intravenous glucose (14.5 mg/kg/min on day 1, increasing to a maximum of 17 mg/kg/min) for 8 days. Insulin levels were markedly increased (129.5 mU/L on day 2) when the concomitant glucose value was 53 mg/dL (at this plasma glucose concentration, insulin levels would normally be <2 mU/L).

Glibenclamide levels were extremely high in the mother’s plasma: 435 ng/mL (measured 4 h after drug intake). Serum samples from the baby showed levels of 9.0 ng/mL glibenclamide on day 3 and 9.8 ng/mL on day 19, suggesting persistent postnatal exposure despite no direct treatment of the infant. This continuing exposure can be explained by the fact that the baby was breastfed, so levels of glibenclamide were also determined in the mother’s milk (7.3 ng/mL on day 3 and 3.1 ng/mL on day 6). Assuming an intake of 150 mL/kg/day and 100% bioavailability, this results in a neonatal exposure of <0.01 mg/day. Postnatal genetic testing excluded the Kir6.2 mutation in the baby. Recovery of mother and newborn was uneventful, and no birth defects were recorded.

CONCLUSIONS
This report describes the presence of macrosomia, severe hyperinsulinemia, and high glucose needs in a KCNJ11 mutation–negative newborn child of a woman with monogenic neonatal diabetes treated with high doses of SU during her pregnancy. Since the mother refused prenatal genetic testing, it was only after birth that the KCNJ11 gene mutation was excluded in the offspring.

Two other women with PNDM due to KCNJ11 mutations who were treated with SU during their pregnancies have been described (8,9). Not surprisingly, given the impact of the KCNJ11 mutation on fetal growth (11), the genotype of the baby is important for the outcome. The first woman (with a Kir6.2-R201H mutation) taking glyburide (40–45 mg/day) had two unaffected children (with diagnosis made postnatally by amniocentesis) (7,8). Both unaffected newborns required early cesarean delivery at 35 and 33 weeks, and had transitory hypoglycemia requiring intravenous glucose administration, but only the second child was macrosomic (2,720 g at 33 weeks [>90th percentile]) (8,9). The recovery was uneventful, and no birth defects were recorded.

The second woman took glibenclamide (60 mg/day) during her entire pregnancy. Genetic testing of cord blood showed the same Kir6.2-E229 K mutation in the fetus as in the mother (9). Cesarean delivery was performed in the 38th week and resulted in a normal birth weight baby girl
child-bearing age with KCNJ11-related diabetes and that close communication among endocrinologists, gynecologists, pediatricians, and geneticists is necessary. Our measurements also show that in a patient on high doses of glibenclamide, glibenclamide can be detected in low amounts in breast milk. This is in contrast to a previous study using less sensitive assays for SUs that did not detect glibenclamide in breast milk of mothers on standard doses (14).

In conclusion, the transplacental passage of large doses of glibenclamide should raise concern, and therapy should be tailored to the genotype of the fetus, especially in the third trimester. Administration of glibenclamide (and other SUs) should be avoided in mothers with KATP-related monogenic diabetes if the baby does not carry the mutation or if prenatal screening has not been performed. In contrast, when the baby is also carrying the mutation, maternal glibenclamide administration may prevent the intrauterine growth restriction usually seen in PNDM newborns.

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**References**