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

Nele Myngheer,[1] Karel Allegaert,[2,3] Andrew Hattersley,[4] Tim McDonald,[4] Holger Kramer,[5] Frances M. Ashcroft,[5] Johan Verhaeghe,[6] Chantal Mathieu,[1,7] and Kristina Casteels[3,8]

Diabetes Care 2014;37:3333–3335 | DOI: 10.2337/dc14-1247

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.

Half of patients with permanent neonatal diabetes mellitus (PNDM) have mutations in the *KCNJ11* and *ABCC8* genes, which encode the two subunits of the β-cell K_{ATP}-dependent potassium channel (Kir6.2 and SUR1, respectively) (1–3). It is important to identify patients with these mutations as the majority can be switched from insulin injections to oral sulfonylurea (SU) compounds, which promote excellent glycemic control that is often significantly improved after the switch (2,4). Achieving good glycemic control during pregnancy is important as it optimizes both maternal and neonatal outcomes (5). The risk of SUs in pregnant women with type 2 diabetes is still unclear, and therefore treatment is often switched to insulin during pregnancy. In women with gestational diabetes, it has been demonstrated that glyburide (9 ± 6 mg/day) is a clinically effective and safe alternative to insulin therapy (6,7). In

[1]Department of Endocrinology, University Hospitals Leuven, Leuven, Belgium
[2]Neonatal Intensive Care Unit, University Hospitals Leuven, Leuven, Belgium
[3]Department of Development and Regeneration, KU Leuven, Leuven, Belgium
[4]University of Exeter Medical School, Exeter, U.K.
[5]University Laboratory of Physiology, Oxford, Oxford, U.K.
[6]Department of Obstetrics/Gynaecology, University Hospitals Leuven, Leuven, Belgium
[7]Department of Clinical and Experimental Medicine, KU Leuven, Leuven, Belgium
[8]Department of Pediatrics, University Hospitals Leuven, Leuven, Belgium

Corresponding author: Kristina Casteels, kristina.casteels@uzleuven.be.

Received 16 May 2014 and accepted 24 August 2014.

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% *o*-phosphoric 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 HbA_{1c} 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 HbA_{1c} level 6.1% [43 mmol/mol], starting HbA_{1c} level 6.1% [43 mmol/mol], HbA_{1c} 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 33 weeks' gestational age, which was reversed by administration of atosiban 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 prenatally 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

(3,010 g). The neonatal period was uneventful: in particular, diabetes did not develop in the child despite having a PNDM mutation.

The literature has been contradictory on whether glibenclamide crosses the placenta to the fetus. Early perfusion studies of the pancreas suggested that, even in high concentrations, glibenclamide did not cross the placenta, but a recent study in 80 subjects with a modern assay has measured cord levels to be 70% on average of maternal blood (12,13). It is unclear whether low (regular) doses of glibenclamide have any effect on fetal growth and postnatal blood glucose concentration. As to high doses of SU, we can hypothesize from this article that even very high doses of glibenclamide are not associated with a birth defect and thus do not seem to affect early fetal development. This is an important point, as patients with *KCNJ11*-related diabetes often have better glycemic control after switching therapy from insulin to SU. It may therefore be preferable to continue the treatment with SU to prevent adverse effects of unstable maternal blood glucose levels on fetal development and this until a genetic diagnosis is performed. Prenatal diagnosis is therefore important: chorionic villus sampling and amniocentesis are possible from the postmenstrual ages of 12 and 15 weeks, respectively. These tests carry a risk of miscarriage in 0.5-1% of women. Noninvasive prenatal testing, whereby fetal DNA from the maternal bloodstream is examined, may soon be available, but some practical (e.g., how early can the test be performed?) and ethical questions remain to be clarified.

If testing cannot be performed or is refused, switching from SU to insulin therapy should be performed by—at the latest—the third trimester. This is important as it is at this time point that high doses of SU can lead to overstimulation of the β-cells and thus to prolonged neonatal hypoglycemia, and can contribute to diabetic fetal macrosomia. It is clear that all these points should be discussed in advance with female patients of 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 K_{ATP}-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.

Funding. K.A. and C.M. are supported by the Fund for Scientific Research, Flanders (fundamental clinical investigatorship). A.H. is a Wellcome Trust Senior Investigator. F.M.A. is supported by the European Research Council (grant 322620).

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

Author Contributions. N.M. researched the data, wrote the manuscript, and approved of its submission for publication. K.A. and C.M. contributed to the discussion, reviewed and edited the manuscript, and approved of its submission for publication. A.H., T.M., and J.V. reviewed and edited the manuscript, and approved of its submission for publication. H.K. and F.M.A. analyzed the drug level, reviewed and edited the manuscript, and approved of its submission for publication. K.C. wrote the manuscript and approved of its submission for publication. K.C. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

References

1. Gloyn AL, Pearson ER, Antcliff JF, et al. Activating mutations in the gene encoding the ATP-sensitive potassium-channel subunit Kir6.2 and permanent neonatal diabetes. N Engl J Med 2004;350:1838–1849

2. Murphy R, Ellard S, Hattersley AT. Clinical implications of a molecular genetic classification of monogenic β-cell diabetes. Nat Clin Pract Endocrinol Metab 2008;4:200–213

3. Hattersley AT, Ashcroft FM. Activating mutations in Kir6.2 and neonatal diabetes: new clinical syndromes, new scientific insights, and new therapy. Diabetes 2005;54:2503–2513

4. Pearson ER, Flechtner I, Njølstad PR, et al.; Neonatal Diabetes International Collaborative Group. Switching from insulin to oral sulfonylureas in patients with diabetes due to Kir6.2 mutations. N Engl J Med 2006;355:467–477

5. Nicholson W, Bolen S, Witkop CT, Neale D, Wilson L, Bass E. Benefits and risks of oral diabetes agents compared with insulin in women with gestational diabetes: a systematic review. Obstet Gynecol 2009;113:193–205

6. Langer O, Conway DL, Berkus MD, Xenakis EM, Gonzales O. A comparison of glyburide and insulin in women with gestational diabetes mellitus. N Engl J Med 2000;343:1134–1138

7. Moretti ME, Rezvani M, Koren G. Safety of glyburide for gestational diabetes: a meta-analysis of pregnancy outcomes. Ann Pharmacother 2008;42:483–490

8. Klupa T, Kozek E, Nowak N, et al. The first case report of sulfonylurea use in a woman with permanent neonatal diabetes mellitus due to *KCNJ11* mutation during a high-risk pregnancy. J Clin Endocrinol Metab 2010;95:3599–3604

9. Gaal Z, Klupa T, Kantor I, et al. Sulfonylurea use during entire pregnancy in diabetes because of *KCNJ11* mutation: a report of two cases. Diabetes Care 2012;35:e40

10. Moors M, Massart DL. Evaluation of solid-phase extraction of basic drugs from human milk. J Pharm Biomed Anal 1991;9:129–139

11. Slingerland AS, Hattersley AT. Activating mutations in the gene encoding Kir6.2 alter fetal and postnatal growth and also cause neonatal diabetes. J Clin Endocrinol Metab 2006;91:2782–2788

12. Elliott BD, Langer O, Schenker S, Johnson RF. Insignificant transfer of glyburide occurs across the human placenta. Am J Obstet Gynecol 1991;165:807–812

13. Hebert MF, Ma X, Naraharisetti SB, et al.; Obstetric-Fetal Pharmacology Research Unit Network. Are we optimizing gestational diabetes treatment with glyburide? The pharmacologic basis for better clinical practice. Clin Pharmacol Ther 2009;85:607–614

14. Feig DS, Briggs GG, Kraemer JM, et al. Transfer of glyburide and glipizide into breast milk. Diabetes Care 2005;28:1851–1855