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

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

[1]Department of Endocrinology, University Hospitals Leuven, Leuven, Belgium

[2]Neonatal Intensive Care Unit, University Hospitals Leuven, Leuven, Belgium Department of Development and Regeneration, KU Leuven, Belgium

[3]University of Exeter Medical School, Exeter, United Kingdom

[4]University Laboratory of Physiology Oxford, Oxford, United Kingdom

[5]Department of Obstetrics/gynaecology, University Hospitals Leuven, Leuven, Belgium

[6]Department of Endocrinology, University Hospitals Leuven, Leuven, Belgium Department of Clinical and Experimental Medicine, KULeuven Belgium

[7]Department of Pediatrics, University Hospitals Leuven, Leuven, Belgium Department of Development and Regeneration, KU Leuven, Belgium

Abstract

Introduction—Sulfonylurea (SUs) are effective at controlling glycemia in permanent neonatal diabetes mellitus (PNDM) caused by *KCNJ11* (Kir6.2) mutations.

Methods—We report the case of a woman with PNDM who continued high doses of glibenclamide (85 mg/d) 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.

Discussion—We hypothesize that high glibenclamide doses in the mother led to transplacental passage of the drug and overstimulation of fetal beta-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 sulphonylureas) 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.

Corresponding author: Kristina Casteels, Department of Pediatrics, University Hospitals Leuven, KU Leuven, Herestraat 49, 3000 Leuven, Belgium, Tel: 003216343801, Fax: 003216343842, Kristina.casteels@uzleuven.be.

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Introduction

Half of patients with permanent neonatal diabetes (PNDM) have mutations in the *KCNJ11* and *ABCC8* genes, which encode the two subunits of the β-cell K_{ATP}-dependent potassium channel (Kir 6.2 and SUR1 respectively)(1,2,3). It is important to identify patients with these mutations as the majority can be switched from insulin injections to oral sulfonylurea (SU) compounds: these promote excellent glycemic control that is often significantly improved after the switch (2,4). Achieving good glycemic control during pregnancy is important as it optimises both maternal and neonatal outcome (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/d) is a clinically effective and safe alternative to insulin therapy (6,7). In PNDM, the high SU doses used are of concern. Two case reports on sulfonylurea use in women with PNDM during pregnancy (3 pregnancies) have been published (8,9). We report the case of a woman with PNDM due to *KCNJ11* mutation where 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

Genetic testing for neonatal diabetes was performed by the department of Molecular Genetics, Royal Devon & Exeter Hospital, Exeter, UK.

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 (ng/mL): 1000, 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 triplicates and within the same batch. Sample aliquots (60 μL) were processed by acidification with 4% ortho-phosphoric acid (60 μL) and C18 reverse phase solid phase extraction and analysis by LC-MS on an Ion Trap mass spectrometer (Amazon, Bruker daltonics) using pseudoSRM 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: (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 been diagnosed with neonatal diabetes at three months of age and had been exclusively treated with insulin (in the assumption 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 a HbA1c of 5.4% (36 mmol/mol). The first baby girl was born vaginally at 38 weeks small for gestational age (weight: 2180g (<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 with diabetic ketoacidosis. Insulin pump therapy was started and genetic testing 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 sulfonylurea and achieved excellent glycemic control.

The second pregnancy was initiated under SU therapy (Glibenclamide 85 mg/d, weight 52 kg (prepregnancy weight), as literature suggested that continuing SU during pregnancy in PNDM should be safe (8,9). This is a high dose of SU, even in non-pregnant patients. Maternal glycemic control during pregnancy was good (mean HbA1c: 6.1% (43 mmol/mol), starting HbA1c: 6.1% (43 mmol/mol), HbA1c at delivery: 6.4% (46 mmol/mol)). Doses of glibenclamide were increased to 90mg/d on the basis of self-monitored glycemias. The mother went into preterm labour at 33 weeks gestational age which was reversed by atosiban and nifedipine; in addition, antenatal betamethasone was given. She was delivered at 33+3/7 weeks by Caesarean section because of ongoing labor and known macrosomia: birth weight was 3600g (>97th percentile) and length 50cm (97th percentile). The baby boy developed hypoglycemia (first measured value was 16 mg/dl) and needed high doses of intravenous glucose (14.5mg/kg/min on day 1, increasing to a maximum of 17mg/kg/min) for 8 days. Insulin levels were markedly increased (129.5 mU/l on day 2) when the concominant 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 hours after drug intake). Serum samples from the baby showed a level of 9.0 ng/ml of 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: these were 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 less than 0.01 mg/day. Postnatal genetic testing excluded the Kir6.2 mutation in the baby. Recovery of mother and newborn were 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 (diagnosed prenatally by amniocentesis)(7,8). Both unaffected newborns required early Caesarian delivery at 35 and 33 weeks and had transitory hypoglycemia needing intravenous glucose but only the second child was macrosomic (2720g at 33 weeks(>90th percentile)) (8,9). The recovery was uneventful and no birth defects were recorded.

The second woman was taking glibenclamide (60mg/day) during her entire pregnancy. Genetic testing of cord blood showed the same Kir6.2-E229K mutation as the mother in the fetus (9). Cesarean delivery was performed in the 38th week and resulted in a normal birth weight baby girl (3010 g). The neonatal period was uneventful: in particular the child did not develop diabetes despite having a TNDM mutation.

The literature has been contradictory on whether glibenclamide crosses the placenta to the foetus. 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 paper 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 from insulin to SU. It may therefore be preferable to continue the treatment with SU to prevent adverse effects of unstable maternal blood sugars on fetal development and this until genetic diagnosis is performed. Prenatal diagnosis is therefore important: chorionic villus sampling and amniocentesis are possible from the postmenstrual age of 12 and 15 weeks respectively. These tests carry a risk of miscarriage in 0.5-(1)%. Noninvasive prenatal testing whereby fetal DNA from the maternal bloodstream is examined may soon be available but some practical (eg how early can the test be done?) 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 beta cells and thus to prolonged neonatal hypoglycaemia 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 between endocrinologists, gynaecologists, paediatricians and geneticists is necessary.

Our measurements also show that in a patient on high doses that glibenclamide can be detected in low amounts in breast milk. This is in contrast to a previous study using less sensitive assays for sulphonylureas 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. Glibenclamide (and other sulphonylureas) 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 may prevent the intrauterine growth restriction usually seen in PNDM newborns.

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Each Author has contributed substantially to the research, preparation and production of the paper and approves of its submission to the Journal. NM researched data and wrote the manuscript. KA contributed to the discussion and reviewed/edited the manuscript. AH reviewed/edited the manuscript. TM reviewed/edited the manuscript. HK analysed the drug level and reviewed/edited the manuscript. FA analysed the drug level and reviewed/edited the manuscript. JV reviewed/edited the manuscript. CM contributed to the discussion and reviewed/edited the manuscript. KC wrote the manuscript.

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References

1. Gloyn AL, Pearson ER, Antcliff JF, Proks P, Bruining GJ, Slingerland AS, Howard N, Srinivasan S, Silva JM, Molnes J, Edghill EL, 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. [PubMed: 15115830]
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. [PubMed: 18301398]
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(9):2503–13. [PubMed: 16123337]
4. Pearson ER, Flechtner I, Njølstad PR, Malecki MT, Flanagan SE, Larkin B, Ashcroft FM, Klimes I, Codner E, Iotova V, Slingerland AS, 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. [PubMed: 16885550]
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. [PubMed: 19104375]
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. [PubMed: 11036118]
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. [PubMed: 18349305]
8. Klupa T, Kozek E, Nowak N, Cyganek K, Gach A, Milewicz T, Czajkowski K, Tolloczko J, Mlynarski W, Malecki MT. 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(8):3599–3604. [PubMed: 20466780]
9. Gaal Z, Klupa T, Kantor I, Mlynarski W, Albert L, Tolloczko J, Balogh I, Czajkowski K, Malecki MT. Sulfonylurea use during entire pregnancy in diabetes because of *KCNJ11* mutation: a report of two cases. Diabetes Care. 2012; 35(6):e40. [PubMed: 22619292]
10. Moors M, Massart DL. Evaluation of solid-phase extraction of basic drugs from human milk. J Pharmaceutical & Biomedical Analysis. 1991; 9(2):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(7):2782–8. [PubMed: 16636122]

12. Elliott BD, Langer O, Schenker S, Johnson RF. Insignificant transfer of glyburide occurs across the human placenta. Am J Obstet Gynecol. 1991; 165(4):807–12. [PubMed: 1951536]

13. Hebert MF, Ma X, Naraharisetti SB, Krudys KM, Umans JG, Hankins GD, Caritis SN, Miodovnik M, Mattison DR, Unadkat JD, Kelly EJ, 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. [PubMed: 19295505]

14. Feig DS, Briggs GG, Kraemer JM, Ambrose PJ, Moskovitz DN, Nageotte M, Donat DJ, Padilla G, Wan S, Klein J, Koren G. Transfer of Glyburide and Glipizide into breast milk. Diabetes Care. 2005; 28(8):1851–5. [PubMed: 16043722]

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