

Persistent Hypocalcemia in a Premature Neonate Exposed to Topiramate *In-Utero*

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ABSTRACT

Neonatal hypocalcemia can result from numerous etiologies and is commonly seen in premature neonates. We describe a late preterm neonate with asymptomatic hypocalcemia whose mother took topiramate throughout the entire pregnancy. Other factors that may contribute to hypocalcemia, including infant of a diabetic mother, were ruled out in our patient. The patient we are reporting on required calcium supplementation for persistent hypocalcemia most likely due to fetal topiramate exposure.

Keywords: Prematurity; Hypocalcemia; Topiramate

INTRODUCTION

During fetal life, nutrients and electrolytes accumulate with increasing gestation, with the most substantial acquisition occurring in the third trimester of pregnancy. During pregnancy, the fetus has an uninterrupted supply of water and electrolytes from the mother transported across the placenta. As gestational age and weight advance, there is an increase in the fetus' intracellular water, protein, fat, calcium, phosphorus, magnesium, and iron content [1]. Calcium plays a critical role in bone mineralization and has functions in cellular signaling and excitability. Interruption of fetal absorption of calcium can lead to hypocalcemia in neonates. Early neonatal hypocalcemia generally occurs in the first 72 hours of life and its etiology may be multifactorial [2,3]. Late onset neonatal hypocalcemia is usually diagnosed 3 days after birth and is commonly secondary to vitamin D deficiency or hypomagnesemia [2,4].

We present a case of a late preterm neonate with asymptomatic persistent hypocalcemia whose mother took topiramate throughout the entire pregnancy. There have been previous reports of *in utero* topiramate exposure impairing parathyroid hormone secretion resulting in hypocalcemic seizures [5]. Although neonatal hypocalcemia can be attributed to many factors, we are reporting on fetal topiramate exposure as the cause of persistent neonatal hypocalcemia. Informed consent to publish has been granted from the patient's guardian.

CASE REPORT

Our patient was a male neonate born to a 33 year old gravida 2 para 2 mother at 34 and 0/7 weeks gestation weighing 2420 grams. Delivery route was vaginal after induction of labor due to poorly controlled type 1 diabetes mellitus. Mother had a complex medical history that included type 1 diabetes mellitus, chronic hypertension, and cerebral thrombosis with cerebral infarction, Moyamoya disease, migraines, seizure disorder, deep venous thrombosis, memory loss, depression and anxiety.

Pregnancy was complicated by hyperemesis gravidarum requiring multiple admissions, type 1 diabetes, and an extensive medication list. The mother's relevant medications during pregnancy included prenatal vitamins, insulin aspart 50 units daily by pump, enoxaparin 160 mg injections daily, buspirone 10 mg by mouth (PO) daily, lamotrigine 300 mg PO daily, levetiracetam 2,000 mg PO daily, topiramate 600 mg PO daily, aspirin 162 mg PO daily, metoclopramide 30 mg PO daily, prochlorperazine 40 mg PO daily, and ondansetron 16 mg PO daily. Mother had topiramate levels drawn at regular intervals beginning in the first trimester of pregnancy until delivery. Topiramate levels were within therapeutic reference range throughout pregnancy, between 2-20 ug/mL. Mother's calcium levels and vitamin D, 25 levels did not drop below reference range throughout pregnancy, 8.9-10.3 mg/dL and 30-80 ng/mL respectively.

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At delivery our patient did not need resuscitation and was directly transported to the neonatal intensive care unit for prematurity. Apgar scores of 7, 8 and 8 were assigned at 1, 5 and 10 minutes respectively. An umbilical venous catheter was placed upon admission and dextrose 10% in water was infused. At 12 hours of life routine basic metabolic panel was drawn with ionized calcium (iCa) of 0.81 mmol/L (reference range 0.95-1.65 mmol/L), his maintenance fluids were then adjusted to contain calcium gluconate 10 mEq/L and a 100 mg/kg calcium gluconate bolus was given. Basic metabolic profiles were checked twice daily with little response to initial calcium gluconate bolus and maintenance fluid infusion, repeat iCa at 26 hours of life being 0.86 mmol/L (Table 1).

Our patient was at risk for hypocalcemia being an infant of a diabetic mother (IDM). The mechanism of hypocalcemia in IDM is likely related to transient effects of a diabetic mother on parathyroid function, or maternal hypomagnesemia caused by urinary magnesium losses leading to fetal magnesium deficiency [6]. On day of life (DOL) 2, iCa was 0.81 mmol/L and magnesium 1.6 mg/dL (reference range 1.7-2.6 mg/dL). A magnesium sulfate bolus of 50 mg/kg was administered and calcium gluconate continued in intravenous fluids. The hypocalcemia observed in our patient was unlikely to be residual effects of maternal diabetes in view of slightly decreased 1.6 mg/dL (reference range 1.7-2.6 mg/dL) and normal (2.0 mg/dL) magnesium levels on DOL 2-3.

Feeds with premature formula Neosure 22 were initiated on DOL 2. Mother's breast milk was not available. On DOL 3, iCa was 0.9 mmol/L, magnesium was 2.0 mg/dL, and phosphorus 6.9 mg/dL (reference range 5.0-9.5 mg/dL), maintenance fluids with electrolytes were continued and feedings were slowly advanced to goal feeds. Although at risk for hypoglycemia, glucose remained stable. On DOL 4 our patient had persistent hypocalcemia (iCa

0.92 mmol/L), he was continued on maintenance fluids containing calcium and monitored closely for symptomatic hypocalcemia (such as muscle spasms, irritability and seizures).

On DOL 6 iCa was 0.85 mmol/L, the patient was given a calcium gluconate bolus, started on a multivitamin 0.5 ml twice daily, vitamin D 400 IU daily and switched to a low phosphate formula to maximize calcium absorption. Despite interventions, persistent asymptomatic hypocalcemia (iCa 0.86 mmol/L) was observed on DOL 7. Calcium carbonate supplementation was started at 80 mg/kg/dose PO every 6 hours (elemental calcium 125 mg/kg/day) and endocrinology was consulted. Pseudohypoparathyroidism or PTH resistance and vitamin D deficiency were investigated. The patient had normal phosphorus levels (6.9 mg/dL, reference range 5.0 - 9.5 mg/dL) and an intact PTH level of 201 pg/mL on DOL 7 which was appropriately increased in response to a calcium of 6.9 mg/dL (reference range 7.5 - 11.0 mg/dL). Per endocrinology, calcitriol 0.25 mcg (0.1 mcg/kg) was initiated and vitamin D increased to 2000 IU daily (1600 IU via cholecalciferol drops and 400 IU via multivitamin) while vitamin D results were pending.

On DOL 11 an improvement in hypocalcemia (1.01 mmol/L) was observed. On DOL 12 continued improvement in hypocalcemia (1.07 mmol/L) and an upward trend in bicarbonate noted that could be attributed to metabolic alkalosis developing from endogenous calcium. Calcium carbonate dose was weaned to 50 mg/kg/dose every 6 hours (elemental calcium 80 mg/kg/day). Endocrinology recommended decreasing vitamin D supplementation from 2000 IU to daily 400IU, in view of 25-Hydroxyvitamin D (25(OH)D) level in normal limits (50 ng/mL, ref range 30-80 ng/mL), and to wean calcium carbonate dosing to the goal of discontinuation. On DOL 14 the iCa normalized to 1.21 mmol/L and calcium supplements were discontinued on DOL 16. Calcitriol was discontinued on DOL 18 when the result of the 1,25-dihydroxyvitamin D3 was

Table 1: Lab values and corresponding management of the neonate.

Collection Time	iCa* (mmol/L)	Mg* (mg/dL)	P* (mg/dL)	Other Lab Values	Management
12 hours of life	0.81	-	-	-	100 mg/kg calcium gluconate bolus; maintenance fluids containing calcium gluconate 10 mEq/L
26 hours of life	0.86	-	-	-	-
DOL* 2	0.81	1.6	-	-	50 mg/kg magnesium sulfate bolus; maintenance fluids containing calcium gluconate 10mEq/L; premature formula
DOL 3	0.9	2	6.9	-	-
DOL 4	0.92	-	-	-	-
DOL 6	0.85	-	-	-	100 mg/kg calcium gluconate bolus, multivitamin 0.5 ml twice daily, vitamin D 400 IU daily
DOL 7	0.86	-	6.9	iPTH* (pg/dL) 201	25 (OH) D* and 1,25 (OH)2D* sent out; calcium carbonate 80 mg/kg/dose PO every 6 hours; calcitriol 0.25 mcg daily, vitamin D increased to 2,000 IU daily
DOL 11	1.01	-	-	-	-
DOL 12	1.07	-	-	25 (OH) D* (ng/mL) 50	Calcium carbonate weaned to 50 mg/kg/dose PO every 6 hours; vitamin D weaned to 400 IU daily
DOL 14	1.21	-	-	-	-
DOL 16	-	-	-	-	Calcium carbonate discontinued
DOL 18	-	-	-	1,25 (OH)2D* (ng/mL) 84	Calcitriol discontinued
DOL 24	1.31	-	-	-	Multivitamin; Preterm formula

*DOL (Day of life); iCa (Ionized calcium); Mg (Magnesium); P (Phosphorus); iPTH (intact PTH); 25 (OH) D (25-hydroxyvitamin D); 1,25 (OH)2D (1,25-dihydroxyvitamin D3)

obtained (84 pg/mL, reference range 31-87 ng/mL). Follow up iCa were obtained up to DOL 24 and the patient was able to maintain his calcium (iCa 1.14- 1.31 mmol/L) on a multivitamin and a standard preterm formula.

DISCUSSION

Early transient neonatal hypocalcemia can result from numerous etiologies including prematurity, IDM, late maturation of the parathyroid axis, pseudohypoparathyroidism, PTH resistance or vitamin D deficiency; all of which were ruled out in our patient. The patient we are reporting on had persistent hypocalcemia normalizing on DOL 14 most likely attributed to topiramate exposure *in utero*.

The exact mechanism of action is not known but topiramate is thought to reduce the duration of abnormal discharges likely by blocking voltage-sensitive sodium channels, enhancing the activity of the inhibitory neurotransmitter gamma-aminobutyrate (GABA), and inhibiting excitatory transmission by antagonizing glutamate receptors, subtype kainite/AMPA (alpha-amino-e-hydroxy-5-methylisoxazole-4-propionic acid) [7,8]. Topiramate is available for oral use, exhibiting rapid absorption and a high bioavailability with peak concentrations at about two hours [7]. Protein binding is low and elimination is primarily renal with 70% of the dose eliminated unchanged in the urine [7]. Minor amounts are metabolized in the liver but when used concomitantly with enzyme inducers (carbamazepine, phenytoin), plasma concentrations of topiramate are halved [8].

Animal studies show transplacental transfer with an increased risk for structural malformations, decreased fetal weights, and reduced skeletal ossification [7]. In humans, cord levels in term neonates were similar to maternal plasma blood levels [9]. Pregnancy registries have revealed fetal harm in human neonates including cleft lip, cleft palate, and classification of small for gestational age (SGA) [7]. Topiramate also transfers into breast milk. Based on an estimated 150 mL/kg/day of breastmilk, infant exposure was calculated as 3–23% of the mother's weight-adjusted dose [9]. There are limited data on the effects of topiramate in breastmilk-fed infants but diarrhea and somnolence have been reported [7,10]. Topiramate has been also been implicated in a report of hypocalcemic seizures in two siblings of separate pregnancies whose mother was treated with topiramate.

This is the second known publication citing an association of prolonged neonatal hypocalcemia with maternal topiramate use.

that correlated with maternal topiramate use [5]. They proposed the hypocalcemia was due to topiramate's effect on protein kinase A leading to a blockage of the calcium-sensing receptor on the parathyroid gland and inducing hypoparathyroidism [5].

CONCLUSION

In conclusion, our patient's PTH was not suppressed yet the patient continued to experience hypocalcemia despite multiple treatment measures. Other causes of hypocalcemia were ruled out and the patient's calcium slowly rose, allowing the discontinuation of calcium supplements by DOL 16. Although the mechanism is currently unknown, we cannot dismiss the association of hypocalcemia with maternal use of topiramate.

CONFLICTS OF INTEREST

None to report.

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