CASE REPORT

Metabolic Acidosis with Ophthalmic Dorzolamide in a Neonate

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Carbonic anhydrase inhibitors are a common cause of normal anion gap metabolic acidosis; however, development is less commonly associated with ophthalmic administration of these agents. We report a case of a premature neonate who was being treated at our institution with betaxolol, dorzolamide, and latanoprost ophthalmic products for suspected bilateral congenital glaucoma. In addition, the patient was also receiving caffeine, ursodiol, and acidified liquid human milk fortifier. The patient developed a normal anion gap metabolic acidosis, and both dorzolamide ophthalmic solution and the acidified human milk fortifier were considered potential causes. Upon discontinuation of the dorzolamide ophthalmic solution and the switching of liquid human milk fortifiers, the normal anion gap metabolic acidosis gradually resolved. As a result of the pH and acidity, the acidified liquid human milk fortifier is thought to be associated with an anion gap acidosis; therefore, dorzolamide is suspected to be the primary cause of a normal gap acidosis. This case demonstrates that systemic effects can occur with ophthalmic administration of dorzolamide in a premature neonate. Ophthalmic agents should not be overlooked as a potential cause of systemic toxicity.

INDEX TERMS: dorzolamide, metabolic acidosis, neonate, ophthalmic administration

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INTRODUCTION

Metabolic acidosis is a common problem in the neonatal intensive care unit (NICU). A metabolic acidosis can be further classified as an anion gap acidosis or a normal anion gap acidosis based on a calculation of the anion gap. An anion gap metabolic acidosis often develops secondary to increased acid production, decreased acid excretion, or toxicity, whereas normal anion gap metabolic acidosis occurs secondary to loss of bicarbonate-rich fluids (e.g., diarrhea, fistula) or renal tubular acidosis (RTA).¹ In addition, iatrogenic causes of normal anion gap metabolic acidosis include acute resuscitation with chloride-rich fluids and administration of medications that inhibit reabsorption of renal bicarbonate (e.g., carbonic anhydrase inhibitors).¹

It is well known that the systemic use of acetazolamide, a carbonic anhydrase inhibitor, increases renal losses of bicarbonate. It does not have a Food and Drug Administration–labeled indication but is commonly prescribed for treatment of metabolic alkalosis.² Development of

metabolic acidosis with topical carbonic anhydrase inhibitors is less common. To date, 1 case report of ophthalmic brinzolamide–induced metabolic acidosis has been described in an adult patient, and 1 case report of ophthalmic dorzolamide–induced metabolic acidosis has been described in a neonate.^{3,4} We report a case of normal anion gap metabolic acidosis in a premature neonate receiving ophthalmic dorzolamide to provide supporting evidence of the systemic effects of ophthalmic preparations and to make clinicians aware that these effects can occur in vulnerable neonatal patients.

CASE REPORT

A 1.275-kg African American male born prematurely via caesarean section at 31 weeks was transferred from an outside hospital to our institution on day of life (DOL) 13 for further evaluation of suspected congenital glaucoma. At the referring hospital he was noted to have an absence of a red reflex during the initial ophthalmic exam, and further workup was conducted.

Table. Selected Laboratory Parameters During the NICU Admission at our Institution

	Day of Life													
	13	14	15	16	17	18	19	21	22	23	24	33	34	40
pH	—	7.28	7.25	7.25	7.29	7.27	7.31	7.28	7.35	—	7.38	—	7.34	—
pCO ₂ (mm Hg)	—	46	46	43	38	38	33	43	42	—	48	—	48	—
HCO ₃ (mEq/L)	—	21	20	19	18	17	17	20	23	—	28	—	26	—
Base excess (mmol/L)	—	-5	-7	-8	-8	-10	-10	-7	-3	—	3	—	0	—
Na (mEq/L)	138	—	—	135	—	134	—	132	134	135	—	138	—	138
K (mEq/L)	4.6	—	—	5.2	—	5.2	—	5.2	5.3	4.6	—	4.6	—	5.8
Anion gap	11	—	—	12	—	11	—	9	8	19	—	8	—	9

NICU, neonatal intensive care unit

The intraocular pressures (IOPs) were noted to be elevated and ranged from 35 to 45 mm Hg (normal IOP in neonate: <24 mm Hg).⁵ Bilateral congenital glaucoma was suspected at the referring hospital, and treatment with betaxolol 0.25% ophthalmic suspension (1 drop in both eyes twice daily), latanoprost 0.005% ophthalmic solution (1 drop in both eyes at bedtime), and intravenous acetazolamide 5 mg/kg/dose (every 8 hours) was initiated. He was also initiated on intravenous caffeine citrate, 5 mg/kg/dose, every 24 hours for apnea of prematurity. As a result of the development of metabolic acidosis at the referring hospital, the intravenous acetazolamide was changed to dorzolamide 2% ophthalmic solution (1 drop in both eyes twice daily) on DOL 2.

The ophthalmology team evaluated the patient upon admission to our institution on DOL 13 and the patient was continued on betaxolol 0.25% ophthalmic suspension (1 drop in both eyes twice daily), dorzolamide 2% ophthalmic solution (1 drop in both eyes twice daily), latanoprost 0.005% ophthalmic solution (1 drop in both eyes at bedtime), and caffeine citrate 5 mg/kg PO (every 24 hours). In addition, his human milk feeds plus Enfamil Human Milk Fortifier Acidified Liquid were continued at approximately 110 mL/kg/day, and the remaining 40 mL/kg/day was provided with a fluid consisting of 10% dextrose, 4% trophamine, and 2 mEq/100 mL calcium gluconate (which provided a total of 4 g/kg/day of protein). On initial labs at our institution the patient was also noted to have a direct hyperbilirubinemia (direct bilirubin, 5.8 mg/dL), thrombocytopenia (platelet count, 109,000/mm³), and normal anion gap metabolic acidosis (Table). Unfortunately, minimal laboratory values were obtained prior to transfer, making it difficult to

assess any trends. The endocrinology and genetics teams were consulted for workup of potential metabolic syndromes because of the presence of cholestasis and normal gap metabolic acidosis. Ursodiol was initiated on DOL 14 at a dose of 10 mg/kg PO every 12 hours for treatment of cholestasis, and the patient was transitioned to full human milk feeds and intravenous fluids were discontinued for the remainder of the hospital stay. At our institution, his feeds were fortified with Enfamil Human Milk Fortifier Acidified Liquid from DOL 13 through DOL 20 and with Similac Human Milk Fortifier (HMF) Hydrolyzed Protein Concentration Liquid from DOL 21 through DOL 40. There was no documentation in the transfer summary of when Enfamil HMF was initiated at the outside hospital.

On DOL 15, IOPs were noted to range from 13 to 14 mm Hg in both eyes while on therapy. Based on the IOPs, the decision was made to discontinue the latanoprost but to continue the dorzolamide and betaxolol. The child's platelet count improved without intervention and was within normal limits by DOL 15; however, the normal anion gap metabolic acidosis persisted (Table). Potential causes of normal anion gap metabolic acidosis (e.g., diarrhea, renal losses) were explored and ruled out, leaving the ophthalmic dorzolamide as the primary suspected cause. Although suspected to be contributing to the metabolic acidosis, the dorzolamide was continued for the management of suspected congenital glaucoma because the benefit was greater than the risk. The Enfamil HMF was also considered as a secondary cause of acidosis as a result of the low pH of the product; however, the fortifier was not changed until DOL 20.

On DOL 21, the ophthalmology team per-

formed an eye exam and determined that the patient did not have glaucoma. The dorzolamide ophthalmic solution was discontinued, but the patient remained on betaxolol per the ophthalmology team because they wanted to continue to monitor his IOP and slowly discontinue the ophthalmic drops as tolerated. He also continued on ursodiol and caffeine therapy. On DOL 21, a normal hepatobiliary iminodiacetic acid scan ruled out biliary atresia. The normal anion gap metabolic acidosis gradually resolved after DOL 21 (Table). The betaxolol was discontinued on DOL 28 because the patient's IOP remained normal. His cholestasis resolved on DOL 32, and he remained in the NICU until he met discharge criteria on DOL 40 (postmenstrual age 37 weeks).

DISCUSSION

This is the second case reported of normal anion gap metabolic acidosis secondary to use of ophthalmic dorzolamide in a neonatal patient. Our case report details the administration of dorzolamide in the inpatient setting to a very low birth weight, premature infant. The previous case report⁴ described a late preterm (35-week gestation) patient receiving dorzolamide ophthalmic solution in the outpatient setting. The dosing of dorzolamide differed between these 2 case reports. Our patient received twice-daily dosing because of his prematurity status, whereas the other patient received the standard dose of 3 times daily.^{4,6} The patient in the previously reported case⁴ developed a profound metabolic acidosis (pH 7.08, PCO_2 31.5 mm Hg, HCO_3^- 9.3 mEq/L, base excess -20.2 mmol/L) after 7 days of therapy. Based on the observed metabolic acidosis in both neonatal cases, it is essential to investigate the potential reasons for this occurrence in this specific patient population.

It is important to first discuss potential etiologies that should be included in the differential when a patient presents with a normal anion gap metabolic acidosis. Known causes of a normal anion gap metabolic acidosis include diarrhea, RTA, adrenal insufficiency, administration of chloride in parenteral nutrition or intravenous fluids, and medications, including non-steroidal anti-inflammatory drugs, potassium-sparing diuretics, and carbonic anhydrase inhibitors.¹ For our case report, all potential causes of a metabolic acidosis were ruled out except for the use of a

liquid HMF and the carbonic anhydrase inhibitor, dorzolamide. Recent reports have suggested that use of acidified liquid HMF is associated with development of metabolic acidosis.⁷ However, this report does not specify whether this is an anion gap or normal anion gap acidosis. These formulations predominantly contain hydrolyzed whey protein, which results in a more acidic solution (pH 4.7) versus powdered fortifier (pH 6.8); therefore, one could speculate that the acidification of this product would likely result in an anion gap acidosis. It has been well documented that carbonic anhydrase inhibitors administered systemically are associated with a normal anion gap acidosis. This occurs because carbonic anhydrase normally catalyzes the conversion of carbon dioxide and water to bicarbonate and hydrogen ions, and inhibition of this enzyme results in decreased bicarbonate reabsorption in the renal proximal tubule and excessive excretion of bicarbonate in the urine. As a result of the bicarbonate loss, a normal anion gap metabolic acidosis occurs.

There is limited information regarding systemic effects from ophthalmic products in neonates; however, it is thought that systemic effects can be observed because of an increase in systemic absorption via the conjunctiva or nasal mucosa and by increased percutaneous absorption in neonates compared to adults. Specifically, it is estimated that the serum concentrations from ophthalmic products in neonates are 20-fold greater compared to those in adults.⁸ In addition, ophthalmic medications are dosed according to a fixed dosing unit of drops. As a result, each drop provides a greater mg/kg dose in smaller patients. The combination of increased absorption, smaller body size and blood volume, and decreased hepatic activity puts neonates at greater risk for systemic effects and toxicity with ophthalmic preparations. Strategies can be implemented to limit the systemic absorption of ophthalmic agents, including compressing the lacrimal sac for 3-4 minutes after administration, administering 1 drop at a time, and immediately wiping off excess overflow from the skin.⁸

We believe that this case demonstrates that significant systemic absorption can occur with ophthalmic administration of dorzolamide in a premature neonate. We used the Naranjo Adverse Drug Reaction Probability Scale to assess the likelihood that dorzolamide ophthalmic

solution was the cause of the normal anion gap metabolic acidosis and calculated a score of “5,” which is deemed “probable.”⁹ The dorzolamide drops and the acidified HMF were discontinued 1 day apart, which may confound the situation. However, as stated previously, it was suspected that dorzolamide was the primary cause because of its known association with development of a normal anion gap acidosis. The acidified HMF would most likely be associated with an anion gap acidosis due to the acidity of the product. However, the addition of the HMF could have augmented the metabolic acidosis caused by the dorzolamide. This case should serve as a reminder to clinicians that significant systemic absorption of ophthalmic preparations can occur and that these medications should not be overlooked when ruling out potential causes of systemic adverse effects. A majority of the ophthalmic preparations were developed and labeled for use in adults and older children. Ophthalmic preparations are fixed-dosage forms (i.e., mg of drug per drop), and smaller children will receive a larger mg/kg dose, putting them at greater risk for increased systemic absorption and toxicity.

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Abbreviations DOL, day of life; HMF, human milk fortifier; IOP, intraocular pressure; NICU, neonatal intensive care unit; RTA, renal tubular acidosis

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