Severe Hypoglycemia Associated With Oral Sotalol Use in Two Children

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Introduction
Hypoglycemia is a rare but recognized side effect of anti-beta-adrenergic medications (beta-blockers) commonly used to manage arrhythmias in children. In 2014 a commercially available premixed solution of sotalol became available, and the use of oral sotalol in children has increased. Hypoglycemia associated with sotalol use has not been previously reported. Sotalol contains a racemic mixture of its D- and L-enantiomers and although it primarily acts to block Ikr (potassium channels), the L-enantiomer has nonselective anti-beta-adrenergic effects. Common sources such as Lexidrugs® and UpToDate®, used to obtain information regarding adverse drug events and precautions, do not list hypoglycemia as a side effect of sotalol. We report 2 unrelated toddlers with severe hypoglycemia, altered mental status, and seizures with sotalol use requiring hospitalization. In both children, hypoglycemia occurred in morning hours after decreased oral intake. Complete work-up for alternative etiologies for hypoglycemia was negative. It is important for prescribing physicians to be aware of this rare but serious side effect and to counsel patients and families appropriately.

Case report
Patient 1
A 2-year-old non-Hispanic White female child was diagnosed with supraventricular tachycardia (SVT) at 6 months of age. She was initially managed with propranolol monotherapy; however, she continued to have breakthrough recurrence. At 14 months of age, propranolol (4 mg/kg/day) was discontinued and sotalol initiated at 150 mg/m² per day divided into thrice-daily (TID) doses. Point-of-care (POC) glucose levels were normal (109–110 mg/dL) during propranolol initiation but were not checked during sotalol initiation. At 21 months of age, owing to recurrence, sotalol was increased to 160 mg/m²/day divided TID. Three weeks later she was admitted to an outside hospital with altered mental status owing to severe hypoglycemia. She was in her usual state of health and had eaten a normal dinner at 8:30 PM the evening prior. Her sotalol was administered as usual at 10 PM. She awoke at 6 AM and was administered her AM sotalol. Although she typically eats a breakfast, she was given a handful of peanuts, then went back to bed. At 7 AM, she awoke screaming and swatting at the air, stating that she was “hitting bugs.” She was described as pale, diaphoretic, appearing dazed and “out of it,” unresponsive to the voice of her mother, who called emergency medical services. She never lost consciousness. Her initial point-of-care glucose by emergency medical services was 32 mg/dL; upon administration of dextrose, she returned back to her baseline self. She was admitted to the outside hospital, where her rhythm remained in normal sinus. Her initial electrocardiogram demonstrated sinus tachycardia with QTc 467 ms. After discontinuing sotalol, she underwent a 24-hour fasting study with production of appropriate ketones without

KEY TEACHING POINTS

- Sotalol is a racemic mixture of 2 enantiomers. In addition to potassium channel blockade, sotalol has nonselective beta-adrenergic blocking effects.
- Severe hypoglycemia can occur with sotalol use, particularly in young children and toddlers after decreased oral intake, after prolonged fasting, or with intercurrent illness.
- Counseling should be provided to parents regarding hypoglycemia risks.

KEYWORDS
Adverse; Altered mental status; Children; Hypoglycemia; Pediatric; Seizure; Side effect; Sotalol

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hypoglycemia (Table 1). Cortisol levels were appropriately elevated, insulin levels low, and growth hormone levels were normal (Table 1). Urine drug levels were negative. Acylcarnitine profile was normal. After testing returned normal, the possibility of hypoglycemia from sotalol was raised; however, as this side effect was not described, she was ultimately diagnosed with idiopathic ketotic hypoglycemia and discharged home on her same dose of sotalol.

Three months later, she was readmitted to our institution for altered mental status and severe hypoglycemia associated with seizures. She was in her usual state of health and had eaten a normal dinner at 7:45 PM the night prior. Sotalol (dose 154 mg/m\(^2\)/day divided TID) was administered at 10 PM. At 6 AM she awoke and was given her sotalol but missed her breakfast and went back to bed. At 7 AM she awoke screaming (parents suspected night terrors) and went back to bed until 8:30 AM, when she awoke agitated, dazed, and unresponsive to voice. She had eye dilation, left eye deviation, and lip smacking (lasting 15–30 seconds), which progressed to tonic-clonic seizures lasting 1.5 minutes. She was taken to the emergency room (ER) by her father, where she was noted to be normothermic, bradycardic (Table 1), listless, and in ketotic hypoglycemia with a POC blood glucose level of 22 mg/dL. Sucrose was administered and

| Table 1 | Data from hypoglycemic episodes |
|---------|--------------------------------|
| Patient 1 | Hypoglycemic episode 1 | Hypoglycemic episode 2 | Patient 2 | Hypoglycemic episode 1 |
| Age | 2.8 years | 3.0 years | 2.5 years |
| Weight/height | 14.2 kg/NA | 14.6 kg/98.5 cm | 12.7 kg/88 cm |
| Sotalol dose | 160 mg/m\(^2\)/day divided TID | 154 mg/m\(^2\)/day divided TID | 173 mg/m\(^2\)/day divided TID |
| Total fasting time prior to episode (hours) | 9.5–10.5 | 12.5 | 20 |
| Temperature (°C) | 36.5 | 36.8 | 35.9 |
| HR (beats/min) | 104 | 69 | 60 |
| RR (breaths/min) | 24 | 28 | 36 |
| BP | 114/86 | 85/42 | 82/40 |
| Serum sotalol (500–4000 ng/mL) | NA | NA | 690 ng/mL |
| POC glucose (mg/dL) | 32 | 22 | <20 |
| Serum glucose (mg/dL) | 60 (post D10) | 21 | |
| pH (venous) | 7.31 | 2.07 (high) | 7.22 |
| Beta hydroxybutyrate (0.02–0.27 mmol/L) | 2.05 (high) | 2.55 (high) | 2.00 (high) |
| Cr (mg/dL) | 0.44 | 0.35 | 0.24 |
| K (mmol/L) | 3.9 | 4.5 | 5.4 |
| Insulin (1.3–40.2 mU/L) | 0.6 (low) | 11.8 | <1.0 (low) |
| C-peptide (0.40–4.5 ng/mL) | 0.01 | 0.9 |
| Lactate (0.2–1.7 mmol/L) | 1.2 | 2.1 | 0.9 |
| Ammonia (22–48 μmol/L) | 26.6 | 19 (low) | <9 (low) |
| Cortisol (3.0–21.0 μg/dL) | 35.46 | 44.1 | 48.9 |
| Growth hormone (<10.1 ng/mL) | 3.04 | 5.9 | |
| Acylcarnitine profile | Free carnitine reduced 15 (range 28–56 μmol/L), otherwise normal | |
| Free fatty acids (≤1.78 mmol/L) | 1.19 | 0.76 | |
| Urine | | | |
| pH | 6.0 | 6.0 | 6.0 |
| Ketones | 15 | 1+ | 1+ |
| Plasma amino acids | Normal | Elevated values likely due to dietary status |
| Ethyl alcohol (mg/dL) | | | |
| IGF-1 (16–135 ng/mL) | 62 | 34 |
| Insulin autoantibody (<0.4 U/mL) | | | <0.4 |
| ICA 512 autoantibody (<5.4 U/mL) | | | <5.4 |
| GAD autoantibody (<5 IU/mL) | | | <5 |
| Newborn screen (1 and 2) | Normal | Normal | |
| Serum drug screen | Negative | Negative | |
| Salicylate | | <1.0 | |
| Urine drug screen | Negative | Negative | |

1 BP = blood pressure; D10 = 10% dextrose; HR = heart rate; NA = not available; POC = point-of-care; RR = respiratory rate; TID = 3 times per day.
1 Listed height in record was not accurate.
1 Normal value 0.
1 Insulin level was not obtained at the time of POC glucose of 22 mg/dL. The glucose level at the time of insulin level of 11.8 mU/L was 275 mg/dL.
1 Overall pattern felt to be normal by endocrine/metabolic team.
she returned quickly to her baseline self. A full endocrine work-up was repeated after discontinuation of sotalol. A 24-hour fast in the intensive care unit produced similar results to her prior admission (Table 1). An overnight electroencephalogram was negative. Sotalol was suspected to be the etiology of her hypoglycemia and was discontinued. She was discharged home on flecainide and has had no further episodes of hypoglycemia in 3½ years of follow-up.

Patient 2
A 2½-year-old non-Hispanic White male child with tuberous sclerosis (TSC2 c.5254 C>T, p.Gln1752Ter, Q1752X) was diagnosed at birth with multiple nonobstructive cardiac rhabdomyomas and Wolff-Parkinson-White syndrome. He had difficult-to-control, refractory SVT within hours after birth. Initial POC and serum glucose was 40 mg/dL, and 65 mg/dL (prior to initiation of beta-blocker) and he was treated with dextrose 10% in water for the first 3 days during initiation of esmolol, then sotalol. Blood glucose levels by day of life 3, following discontinuation of dextrose 10% in water, were normal (72–90 mg/dL). He was treated with esmolol, which was discontinued to initiate intravenous (IV) sotalol. Subsequently he transitioned to oral sotalol followed by addition of propranolol. With the exception of a single serum level of 68 mg/dL on sotalol 165 mg/m²/day for which no mention of propranolol. With the exception of a single serum level of 68 mg/dL on sotalol 165 mg/m²/day for which no treatment was administered, his glucose levels were normal. He was ultimately discharged home on dual-therapy propranolol (3 mg/kg/day) and sotalol (200 mg/m²/day). Blood glucose levels on dual therapy ranged from 87 to 90 mg/dL. While at home, he was developing normally for age and had no history of seizures.

At the age of 2½ years, his parents self-discontinued propranolol after they noted him “looking drunk,” which they attributed to low blood sugar (blood glucose levels were not checked but symptoms resolved after he was given ice cream). Three months later, he was admitted with severe hypoglycemia associated with seizures. At the time of the event, the patient was on monotherapy sotalol at a dose of 173 mg/m²/day divided TID. He was on no other medications. The day prior, he was in his usual state of health and had spent the afternoon at a camping area with his father. His father reported he was very active and ate a large late lunch around 3 PM. He may have had some snacks around 8 PM but did not eat a full dinner that night and went to bed next to his father. In the morning, the patient awoke at 10 AM and seemed his usual self. His father administered his 10 AM sotalol dose. Both fell back asleep. One hour later, while still in bed, his father awoke and described the patient as lethargic, irritable, and “acting drunk.” Abnormal arm movements with clenching of the right fist and eyes deviated rightward were noted. He was unresponsive to his father’s voice and was therefore driven to the ER. In the ER he was hypothermic (Table 1), lethargic, and unresponsive to sternum, with leftward eye deviation, left-sided hyperreactivity, and nystagmus. His rhythm was sinus bradycardia with a QTc of 461 ms. His initial serum blood glucose was 21 mg/dL; critical labs were sent at the same time. He was given 2 boluses of D10, lorazepam, and a levetiracetam load with resolution of his seizures, bradycardia, and hypothermia. He became responsive and arousable but remained tired, appearing postictal for several hours before he returned completely to baseline. Head computed tomography and electroencephalogram demonstrated no abnormalities. There were no concerns regarding accidental ingestion of sotalol or any other substances. To assess possibility of sotalol toxicity given higher maintenance dosing, a sotalol level was sent (drawn 6 hours after his 10 AM dose) and was within normal therapeutic limits (Table 1). Critical labs demonstrated a normal response with low insulin, normal growth hormone, and elevated cortisol levels. Serum and urine drug levels were negative. Acylcarnitine profile was normal. Although his parents reported no viral symptoms, he did develop a low-grade fever (temperature 38.7°C) on hospital day 2. Viral panels returned positive for adenovirus and rhinovirus. Complete work-up by neurology and endocrinology were negative. Sotalol was discontinued and he was discharged home on flecainide, with no further episodes of hypoglycemia or seizures in 1-year follow-up.

Discussion
We report 2 cases of severe hypoglycemia and seizures in 2 children being treated with higher doses of oral sotalol. At the time of the hypoglycemic episodes, both children were on monotherapy sotalol (Sotylize®) with no evidence of accidental overdose. In patient 2, the sotalol level was confirmed to be in therapeutic range at the time of hypoglycemia.

In both cases, thorough investigation of other etiologies of hypoglycemia was performed and found to be negative in both children. Both families had experience recognizing SVT and neither felt episodes were associated with recurrence. The prolonged altered mental status without frank loss of consciousness, documented sinus rhythm during symptoms in patient 2, and borderline QTc measurements argued against ventricular arrhythmias. Although patient 2 had tuberous sclerosis, which can rarely be associated with insulinoma, he had adequate ketone production during hypoglycemia.

Notably, neither child had severe hypoglycemic episodes while being treated with propranolol, although episodes were suspected in patient 2. The reported incidence of fasting hypoglycemia among pediatric-aged children greater than 6 months in the general population is 0.034%. The rate of hypoglycemia among all children taking beta-blockers is not known; however, limited studies have reported an incidence of 0.5% among infants administered propranolol for infantile hemangiomas and 3% among beta-blocker-treated children with long QT syndrome. In this large study of long QT syndrome children by Poterucha and colleagues, 9 children with hypoglycemic events were being treated with nadolol or propranolol, 6 of whom had associated seizures. The mean age of the children was 3.5 years ± 2 years, with all events occurring after decreased caloric intake and 3 during a viral illness.
Episodes were also commonly noted in morning hours.\textsuperscript{3} There have been no reports of hypoglycemia associated with IV or oral sotalol administration. Studies from our own center evaluating safety of both high-dose oral sotalol in 78 neonates and infants (median age 24 days, range 3–728 days) and IV sotalol in 47 children (median age 2 years, interquartile range 0.07–10.03 years) demonstrated no reported episodes of severe hypoglycemia during initiation requiring intervention.\textsuperscript{4,5} In addition, a study of high-dose propranolol at our institution demonstrated no documented severe hypoglycemia requiring intervention among 287 infants initiated at less than 1 year of age (median age 17 days, interquartile range 6–33 days).\textsuperscript{6} Both patients in this case report were on higher doses of sotalol (154 and 173 mg/m\textsuperscript{2}/day) and in both cases, events occurred well after initiation. Thus, while prior studies from our institution did not demonstrate hypoglycemia during sotalol initiation,\textsuperscript{4,5} we should be cognizant that higher doses of sotalol may increase hypoglycemia risks and caution should be continued even during outpatient follow-up.

Although the exact mechanism of beta-blocker-induced hypoglycemia remains unknown, sotalol is a class III antiarrhythmic that also has noncardioselective anti-beta-adrenergic properties similar to propranolol and nadolol. The presentations of these 2 cases are similar to multiple reports of anti-beta-adrenergic-related hypoglycemia in literature.\textsuperscript{7,8} Glucose homeostasis involves a complex interplay between insulin, catecholamines, growth hormone, cortisol, food intake, and glucose disposal. Children have higher metabolic requirements and lower glycogen stores when compared to adults and thus may be more susceptible to hypoglycemia.\textsuperscript{9–11} Although it is possible severe hypoglycemia in these 2 patients was coincidental, our work-up suggests that drug-induced effects likely contributed in both patients. We suspect hypoglycemia secondary to sotalol is most likely provoked by a combination of metabolic stressors such as decreased caloric intake, prolonged fasting, or undiagnosed infection, in combination with nonselective anti-beta-adrenergic use in young children who may have an underlying susceptibility.

These 2 cases illustrate the potential for severe hypoglycemia in children treated with sotalol and consideration should be given to list hypoglycemia as a potential side effect of sotalol administration. For children who have had prior hypoglycemia episodes on propranolol, who have options for alternative treatment, we suggest that sotalol should be avoided. Flecainide may be a better choice for children susceptible to beta-blocker-associated hypoglycemia. Clinicians, particularly sotalol prescribers or those that evaluate hypoglycemia, should also be aware of this rare but potentially serious adverse event. These events appear to be most common in younger children who may not be able to verbalize symptoms. Additionally, beta-blockers may mask typical clinical symptoms of hypoglycemia such as tachycardia and diaphoresis, making it more difficult for parents to identify early warning signs and symptoms. Hence, even among children who have never had hypoglycemic events, counseling and education should be provided to parents regarding the risks, signs and symptoms, and guidance to avoid hypoglycemia, particularly in young toddlers. In young children, prolonged fasting should be avoided and consideration should be given to administer morning doses with or immediately following food administration. Higher doses of sotalol in young children may also contribute to risk. With adequate recognition and counseling, future events may be preventable.

**Conclusion**

Severe hypoglycemia is rare but may be associated with sotalol use, particularly in young children during early morning hours after decreased caloric intake or intercurrent illness. Physician recognition of this side effect and appropriate parental counseling may help prevent episodes.

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