Case Report of Successful Treatment of Pallid Breath-Holding Spells With Glycopyrrolate

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abstract

Breath-holding spells are a common childhood disorder that typically present before 12 months of age. Whereas most cases are benign, some patients have very severe cases associated with bradycardia that can progress from asystole to syncope and seizures. Treatment studies have implicated the use of several therapies, such as oral iron, fluoxetine, and pacemaker implantation. This is a retrospective study of patients treated with glycopyrrolate for pallid breath-holding spells. Clinical data from 4 patients referred to pediatric cardiology who saw therapeutic benefit from treatment using glycopyrrolate were reviewed to evaluate for clinical response to the drug. Two twin patients, whose symptoms began at 5 months of age, experienced a decrease in breath-holding frequency after 1 month. A patient diagnosed at 7 months of age experienced a decrease in frequency of spells. A patient diagnosed at 10 months of age reported cessation of syncope shortly after initiation of glycopyrrolate and complete resolution of breath-holding spells during prolonged treatment. This case study of 4 patients with pallid breath-holding offers evidence that glycopyrrolate may be beneficial in treating breath-holding spells and has a safer side-effect profile than pacemaker implantation.

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Breath-holding spells are a common pediatric disorder, usually occurring between 6 months and 4 years of age.[1] The spells, characterized as nonepileptic, paroxysmal anoxic syncope that often leads to seizures, are provoked by external emotional stimuli, such as pain, anger, crying, or excitement. Breath-holding spells are classified into 3 types based on a child's coloration: cyanotic, pallid, or mixed.[2] The cause is unknown, but a genetic pattern of autosomal dominance with variable penetrance has been identified.[3]

Diagnosed clinically, breath-holding spells are described as a sequence of emotional provocation, noiseless expiration accompanied by apnea, color change, and syncope resulting from autonomic dysfunction.[2] Although autonomic dysfunction is the common underlying problem, cyanotic breath-holding spells result from overactivity of the sympathetic nervous system, whereas pallid breath-holding spells are the result of increased parasympathetic tone.[4] The natural course of breath-holding spells is usually transient, with cessation by early toddler years.[5] Long-term prognosis is generally excellent, with the expectation of normal development. The standard of care is reassurance for most patients, but children with severe sequelae require further treatment.

Various medical treatments have been studied. Walsh et al reported that fluoxetine decreased the frequency of breath-holding spells in 5 of 6 patients, with complete resolution in 3 patients.[4] Iron-deficiency anemia has also been linked to breath-holding spells, with

complete or partial remission of symptoms in 84% of patients treated with iron sulfate.[6] In severe cases, permanent pacing has been used as treatment of prolonged bradycardia and asystole.[1]

A few clinicians have noted anecdotal success in the treatment of breath-holding spells with anticholinergic agents, including glycopyrrolate. Normally used in anesthesia to reduce oral secretions, glycopyrrolate is a synthetic anticholinergic drug with longer-acting properties than atropine that provides treatment against cardiac inhibition in severe recurrent breath-holding spells.[5] In 1 case report, the use of glycopyrrolate resulted in resolution of syncope in 1 patient with severe recurrent spells without the significant side effects seen with cardiac pacemaker implantation.[5] In our retrospective study, we examine the use of glycopyrrolate in 4 patients with similar recurrent syncope and bradycardia and report that glycopyrrolate is beneficial and is an alternative treatment modality.

METHODS

This retrospective case series was conducted with the approval of the Institutional Review Board at the Medical University of South Carolina. Since January 1, 1990, all patients have been referred to the Children's Heart Center of South Carolina for cardiovascular evaluation of severe, recurrent breath-holding spells.

RESULTS

Patient 1

Patient 1 is a male whose symptoms of breath-holding began at 7 months of age, characterized by episodes of tensing and relaxing, associated with syncope. His spells lasted for ~30 seconds. A 24-second pause was documented on Holter monitor. Electrocardiograms (ECGs) showed normal sinus rhythm. He was diagnosed at 7 months of age and was previously treated with a multivitamin. After other unsuccessful therapies, he was initiated on glycopyrrolate at 24 months of age. He experienced a mild decrease in frequency of episodes, but did not tolerate the side effects of glycopyrrolate, experiencing dry mouth. He later underwent epicardial pacemaker implantation with a single-chamber VVI with hysteresis mode.

Patient 2

Patient 2 is a female whose symptoms of breath-holding began at 5 months of age, characterized by mixed spells, loss of consciousness, and prolonged tonic-clonic seizures. These events occurred 8 to 10 times daily. She was diagnosed with breath-holding spells at 14 months of age and was previously receiving a multivitamin with iron. ECG showed sinus tachycardia. She did not have documented spells on Holter monitor, but her events were severe and associated with seizure. She was initiated on glycopyrrolate at 14 months of age at a dose of 0.75 mg 3 times per day (TID) and experienced improvement in the frequency of her events within 1 month (Fig 1). Nevertheless, given the severity of her seizures, she later underwent epicardial pacemaker implantation via subxyphoid incision with a single-chamber VVI pacemaker.

Patient 3

Patient 3 is a female whose symptoms of breath-holding began at 5 months of age, characterized by mixed spells and loss of consciousness. These events occurred 8 to 10 times daily. She was diagnosed with breath-holding spells at 14 months of age and was previously taking a multivitamin. ECG showed sinus tachycardia. She was initiated on glycopyrrolate (1 mg TID) at the time of diagnosis. She remained on treatment for ~1 month and experienced a decrease in frequency of breath-holding spells. She later underwent epicardial pacemaker implantation via subxyphoid incision with a single-chamber VVI pacemaker.

Patient 4

Patient 4 is a male whose symptoms of breath-holding began at 9 months of age, characterized by cyanosis, back arching, stiffening, eyes rolling back, and unresponsiveness. ECG showed sinus tachycardia. He was diagnosed with breath-holding spells at 10 months of age, and glycopyrrolate was initiated at 0.25 mg TID. He improved with decreased frequency of spells within 1 month of treatment. His dose was titrated up over time to 1 mg each morning and afternoon and 0.5 mg each evening. Given side effects of constipation and decreased appetite, his dose was titrated down to 1 mg twice daily ~10 months into his treatment, which resulted in a few episodes of cyanosis but no syncope. Over the course of 17 months of treatment, he experienced cessation of both bradycardia and syncope. On the higher doses daily, he still experienced some constipation and was subsequently switched to fludrocortisone (Florinef) 0.1 mg daily.

DISCUSSION

Breath-holding spells occur in 0.1% to 4.6% of children and have affected children for hundreds of years.[2] Bridge et al[7] and Lombroso and Lerman[8] have identified that the onset usually occurs before 12 months of age. Our study population was consistent with epidemiologic data and inheritance patterns of breath-holding spells. Twins were similarly affected in 1 family. Another family had a history of breath-holding spells in both parents as infants.

The mainstay of treatment is reassurance, as breath-holding spells typically carry a favorable prognosis with normal development.[9] Having daily severe, recurrent episodes is anxiety provoking for parents and can be life-threatening for patients. Many

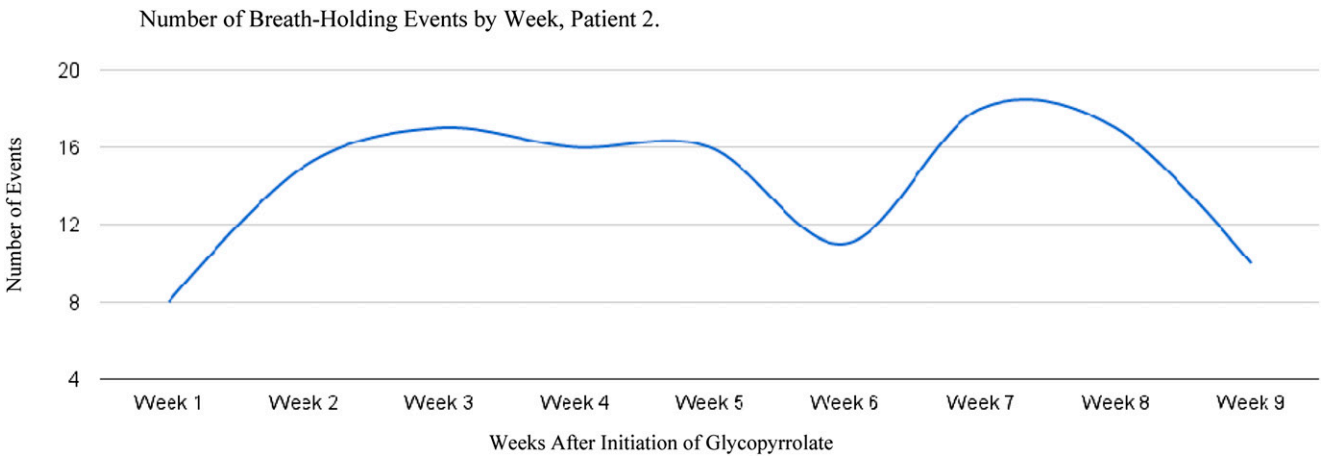

FIGURE 1
Number of breath-holding events by week, patient 2.

therapies aim to improve sequelae. Various treatments, including atropine, have been shown to be beneficial in some children, but their benefits have also been inconsistent.[2,10] Although pacemaker implantation has shown to be beneficial in patients with severe disease, implantation does have risks, for example, lead failure and infection of the device. Kelly et al identified permanent pacemaker implantation as efficacious in treating severe cases, but patients were at risk for refractory spells, multiple revisions, lead retraction, and end of battery life.[11]

A recent case study suggested the use of glycopyrrolate, given the resolution of symptoms without side effects. In Carano et al, a 13-month-old patient was successfully treated with a combination of glycopyrrolate and theophylline, with resolution of severe recurrent pallid breath-holding spells.[5] Glycopyrrolate is a synthetic quaternary ammonium compound, known for its antimuscarinic effects.[12] Given its properties, including being highly ionized, glycopyrrolate has variable absorption in the gastrointestinal tract and does not cross the blood–brain barrier. In a study of 6 pediatric patients given 50 μg/kg glycopyrrolate, oral administration yielded very low plasma concentrations that lasted up to 12 hours. The mean time to reach maximum concentration was 90 minutes, with a mean bioavailability of 3.3%.[13] Originally synthesized in 1960, glycopyrrolate was used to treat peptic ulceration and has also been used during anesthesia for its effects as an antisialogue and to stabilize heart rate variability with reversal agents.[12,14] Like many drugs, glycopyrrolate affects multiple processes, owing to its actions on multiple receptors in different organs, such as the heart. It is known that spinal anesthesia causes bradycardia. The anticholinergic properties of glycopyrrolate block the end-organ effects of the vagus nerve, thus reducing the risk of bradycardia with the reversal of neuromuscular blockade.[15] Studies have demonstrated that glycopyrrolate at lower doses causes an increase in contraction of atrial myocardium by 4% to 13%, and also that the drug antagonizes depressant effects of muscarinic agonists, such as acetylcholine. Radioligand studies show that glycopyrrolate is a potent inhibitor at the M1 and M2 receptors with a preference for the M2 subtype, located in the heart.[12] Some literature suggests premedication of children who are susceptible to bradycardia in effects surrounding anesthesia, as glycopyrrolate blocks cholinergic insults to the heart. This mechanism is similar to patients with pallid breath-holding spells who suffer from autonomic dysfunction with overactivity of their parasympathetic nervous system causing bradycardia, syncope, and in some cases, seizures.

Our data suggest that breath-holding spells can be safely treated with glycopyrrolate. One limitation in our study is the natural course of spells to resolve over time, which is a possibility in the patient treated for 17 months. Another limitation is the retrospective nature of the study, which lends itself to inconsistencies in data acquisition and recording. It is important to counsel patients about the side effects of anticholinergic drugs such as glycopyrrolate, which may include constipation, dry mouth, and behavioral changes. These side effects are more frequent at higher doses.[16] The side effects of glycopyrrolate could possibly be minimalized by increasing the frequency of administration at lower doses or in shorter treatment intervals. It is important to explain that spells may not completely resolve on medical therapy, but that spells may decrease to a more tolerable frequency. To further evaluate efficacy of the use of glycopyrrolate, a large randomized controlled trial is needed to provide more definitive data on the most

therapeutic dose of the drug, the time to improvement, and the optimal age of administration.

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