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.
complete or partial remission of
symptoms in 84% of patients treated
with iron sulfate. In severe cases,
permanent pacing has been used as
treatment of prolonged bradycardia
and asystole. 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-staying properties than
atropine that provides treatment
against cardiac inhibition in severe recurrent breath-holding spells. In a 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. 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 cyanosis,
tensing and relaxing, associated with
syncope. His spells lasted for
approximately 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
anterograde 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
anticholinergic medication. 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 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 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
fluorocortisone (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. Bridge et al7 and Lombroso and
Lerman8 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. Having
daily severe, recurrent episodes is
anxiety provoking for parents and can
be life-threatening for patients.
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. 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.

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. Glycopyrrolate is a synthetic quaternary ammonium compound, known for its antimuscarinic effects. 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%. Originally synthesized in 1960, glycopyrrolate was used to treat peptic ulceration and has also been used during anesthesia for its effects as an antisialagogue and to stabilize heart rate variability with reversal agents. 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. 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. 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. 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

![Number of Breath-Holding Events by Week, Patient 2.](http://pediatrics.aappublications.org/)

**FIGURE 1**

Number of breath-holding events by week, patient 2.
therapeutic dose of the drug, the time to improvement, and the optimal age of administration.

REFERENCES


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

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