Glycopyrrolate and Theophylline for the Treatment of Severe Pallid Breath-holding Spells

abstract

Severe pallid breath-holding spells (BHSs) are based on parasympathetic hyperactivity, leading to cardiac asystole, pallor, brain ischemia, loss of consciousness, and reflex anoxic seizures. In recent years, an increasing number of patients with severe pallid BHSs have been successfully treated with pacemaker implantation. We present the case of a 13-month-old girl suffering from repeated severe pallid BHSs, causing asystole, loss of consciousness, and generalized anoxic seizures. She underwent treatment with oral glycopyrrolate, an anticholinergic drug, and an oral retard preparation of theophylline. The aim of the treatment was to decrease cardiac inhibition with glycopyrrolate and to bring about a positive chronotropic effect with theophylline. In our case, the combined therapy was effective in suppressing syncope and reflex anoxic seizures associated with BHSs. This avoided the need for ventricular pacemaker implantation.

Pediatrics 2013;131:e1280–e1283

AUTHORS: Nicola Carano, MD, Ilaria Bo, MD, Elena Zanetti, MD, Bertrand Tchana, MD, Giulia Barbato, MD, and Aldo Agnetti, MD

Pediatric Cardiology, Department of Pediatrics, University of Parma, Italy

KEY WORDS
breath-holding attack, syncope, asystole, seizure

ABBREVIATIONS
BHS—breath-holding spells
ECG—electrocardiogram

doi:10.1542/peds.2012-0182

Accepted for publication Dec 14, 2012

Address correspondence to Nicola Carano, MD, Department of Pediatrics, University of Parma, Via Gramsci 14, 43126 Parma, Italy. E-mail: nicola.carano@unipr.it

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275). Copyright © 2013 by the American Academy of Pediatrics

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: No external funding.
Severe pallid breath-holding spells (BHSs) are a well-recognized clinical entity occurring in infancy and preschool years. After emotional stress (anger, fright, frustration, pain), the subject typically starts crying, then becomes apnoic and pallid, loses consciousness, falls to the floor, and shows tonic muscular contractions and clonic movements. The mechanism is based on parasympathetic hyperactivity, leading to cardiac asystole and cerebral ischemia that is responsible for the loss of consciousness and reflex anoxic seizure. Because of the benign nature and natural history of these spells, which are transient and disappear during preschool years, an explanation of the event and reassurance of the parents is sufficient in the majority of cases. However, a few individuals suffer from frequent, severe pallid BHSs and reflex anoxic seizures that have a strong impact on the lifestyle of both the child and his or her family. In these cases, cardiac pacemaker implantation has been successfully performed. We present a case of severe recurrent pallid BHS and reflex anoxic seizures in a patient in whom a combined treatment with glycopyrrolate and theophylline was effective and avoided the need for cardiac pacemaker implantation.

CASE REPORT

A 13-month-old girl (weight 9.3 kg) presented with several episodes of BHSs. At least 15 episodes followed by syncope had occurred within a 6-month period. These spells were precipitated by pain after minimal trauma or, more frequently, emotional stress and were characterized by short apnea, pallor, and syncope (usually lasting <1 minute). She was admitted to the hospital for a spell that began after an anger attack and was characterized by noiseless crying, short apnea, pallor, and syncope accompanied by stiffness, arching of the back, rolling back of the eyes, and clonic activity. The seizure lasted 4 minutes, and the patient appeared to be confused for the next 15 minutes. Except for the BHS, the patient’s history was uneventful. Physical examination did not show any abnormality. Familial history included that the mother and her brother had suffered from both cyanotic and pallid BHSs without syncope. A maternal aunt had suffered from many pallid BHSs with syncope. Standard electrocardiogram (ECG), QTc measurement, echocardiography, encephalography, and brain MRI were all found to be normal. Iron deficiency was ruled out. Oral atropine sulfate was started at 0.01 mg/kg twice daily, but no beneficial effects were observed. A new pallid BHS followed by syncope and a seizure lasting 5 minutes occurred during the 24 hours of ECG monitoring. During this episode, a 25-second period of asystole was recorded (Fig 1), confirming the diagnosis of reflex anoxic seizure. Several shorter asystolic periods (4–6 seconds) were recorded during other episodes of BHS without syncope. No tachyarrhythmias were detected, and the mean heart rate was 117 bpm.

We discussed this case on pediheart@pediheart.net. A dozen experts in the field of BHSs participated, and the majority suggested implanting a ventricular pacemaker, but one suggested using oral theophylline and/or a transdermic scopolamine patch and another proposed glycopyrrolate, an anticholinergic drug with a longer action than atropine. The implantation of a ventricular pacemaker was debated, but because BHSs normally disappear with growth and the parents were worried about implant-related risks and opposed immediate pacing, we decided to reserve the pacemaker as the final option and try additional medical treatment. The available transdermic scopolamine patch was considered too difficult for our patient to handle. We started treatment combining oral glycopyrrolate (0.5 mg three times daily, 8 AM, 12 PM, 4 PM) and an extended-release formulation of anhydrous theophylline that permits a single oral administration every 12 hours (80 mg twice a day). This combined approach was chosen with the aim of decreasing cardiac inhibition with glycopyrrolate, while producing a positive chronotropic effect and stimulating the medullary respiratory center with theophylline. The schedule of the glycopyrrolate was planned to maximize drug activity during waking hours. The combined therapy (the dose of glycopyrrolate was increased to 1 mg three times daily when the patient’s weight exceeded 10 kg) was continued and found to be effective. The patient continued to present pallid BHS (mean frequency of 1 episode per week), but neither syncope nor seizure occurred. Holter ECG monitoring was performed 3 times after starting treatment; mean heart rate ranged from 131 to 134 beats per minute. No BHS occurred during ECG monitoring. As the patient grew, the frequency of BHS progressively decreased so that when she was 30 months old, theophylline was discontinued. In the following 6 months, the patient’s reactivity to the situations that had usually triggered BHS spells changed; she no longer presented BHS, and when she was 3 years old, glycopyrrolate administration was discontinued. The patient was followed for 1 year after stopping the treatment, and no additional BHS occurred.

DISCUSSION

A BHS can occur at any time after birth with peak onset between 6 and 12 months. Approximately 50% of children experience termination of spells by age 42 months and the remainder by 7 to 8 years. As in our case, a positive family history is often observed, consistent with an autosomal dominant trait transmission with incomplete penetrance.
A number of medical treatments have been reported: iron has been used in cyanotic BHSs associated with iron deficiency\textsuperscript{16}; anticholinergic drugs such as atropine and scopolamine have been used to antagonize vagal hyperactivity and the subsequent cardiac inhibition\textsuperscript{1}; theophylline has been used for its positive chronotropic effects and capacity to stimulate the medullary respiratory center\textsuperscript{1}; piracetam has been proposed in hyperactive children with BHS\textsuperscript{17}; clonidine\textsuperscript{18} and tetrabenazine\textsuperscript{19} have been considered useful in cyanotic BHS; and ventricular pacemaker implantation has shown great effectiveness in suppressing symptoms in patients with severe and frequent spells associated with asystole or severe bradycardia and reflex anoxic seizures.\textsuperscript{7–13}

Pacemaker implantation is currently a safe procedure in small children; the devices are small and can be removed if necessary. Therefore, in severe pallid BHS with syncope and prolonged asystole, pacing is a successful option that should be proposed to parents.\textsuperscript{7–9,12}

We decided not to implant a ventricular pacemaker for 4 reasons: the parents were against immediate pacing, they were highly motivated and cooperative in following medical treatment, BHS is a transient phenomenon, and the attribution of deaths to BHS remains controversial.\textsuperscript{19–23}

In our case, similar to the situation in certain types of neurocardiogenic syncope, pallid BHS determined cardiac inhibition and asystole, signifying parasympathetic hyperactivity. Therefore, an anticholinergic drug such as atropine seemed to be a reasonable choice but was unfortunately ineffective. Believing that an anticholinergic drug would be effective, we decided to try glycopyrrolate, a synthetic anticholinergic drug that is longer acting than atropine. This choice was based on a personal communication about the efficacy of this drug in pallid BHS (personal communication, J.P. Saul, Children's Hospital of the Medical University of South Carolina, 2009). Glycopyrrolate is commonly used in anesthesia to reduce salivary, tracheobronchial, and pharyngeal secretions.\textsuperscript{24} It is off label for those <3 years of age and is approved only for severe drooling.\textsuperscript{24,25} Common side effects are a reduction in the ability to sweat, fever, dry mouth, dry eyes, constipation, vomiting, and headaches.\textsuperscript{24}

Theophylline is known for its chronotropic effect. The aim of the approach used in this case was to decrease cardiac inhibition with glycopyrrolate and to produce a positive chronotropic effect with theophylline. The other effects of theophylline on the medullary respiratory center were probably not relevant in this case.

In conclusion, we observed a resolution of syncopal attacks and reflex anoxic seizures, without side effects. In our case, the combined treatment avoided the need for ventricular pacemaker implantation. Because the natural history of BHS is to improve with age, some of the improvement observed in this patient may have been related to this fact. A placebo effect cannot be ruled out.

Oral treatment with glycopyrrolate and theophylline represents an alternative therapy in some patients with severe pallid BHSs. Because of the small number of patients suffering from pallid BHSs, a multicenter controlled study is required to further evaluate the efficacy of this treatment. In contrast to our method, a cardiac event monitor rather than a 24-hour ECG monitor may be more useful in recording an ECG during a BHS in patients who do not present frequent episodes.

**REFERENCES**

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**FIGURE 1**

ECG Holter monitoring during a pallid BHSs showing a 25-second cardiac asystole. During this episode, the patient presented syncope and reflex anoxic seizure (on this strip, paper velocity is 5 mm/sec).
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DOI: 10.1542/peds.2012-0182 originally published online March 18, 2013;
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