Treatment of Autonomic-Mediated Orthostatic Intolerance in Children and Adolescents
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Syncope or near-syncope spells are a relatively common occurrence in older children and adolescents. It has been estimated that 15-30% of adolescents will have at least one episode of syncope before reaching adulthood, with approximately half having multiple episodes. Orthostatic intolerance, recurrent syncope or near-syncope when rising from a seated or lying position, may have an autonomic, cardiac, neurologic, psychiatric, or metabolic cause, or may be idiopathic. Approximately 70-75% of patients are diagnosed with autonomic-mediated orthostatic intolerance. This category includes common vasovagal syncope, as well as postural orthostatic tachycardia syndrome and orthostatic hypotension.\(^1\)\(^5\)

Postural orthostatic tachycardia syndrome (POTS) is defined as syncope or near-syncope associated with dizziness, weakness, and tachycardia (an increase in heart rate of 30 bpm or more in the absence of hypotension) upon standing. In some patients, it has been associated with chronic fatigue after a triggering illness such as Epstein-Barr virus. The incidence of POTS in children and adolescents is much greater than that of orthostatic hypotension. In a recent analysis of 142 children diagnosed with orthostatic intolerance, autonomic testing identified POTS in 71% and orthostatic hypotension in only 5%.\(^2\)

Most children and adolescents diagnosed with autonomic-mediated orthostatic intolerance need only education on maintaining adequate hydration, increasing dietary sodium intake, and removing known triggers.\(^1\)\(^3\) Counter maneuvers (sitting or lying down when symptomatic) and conditioning exercises are also beneficial. Patients with recurrent syncope or orthostatic hypotension, however, may require additional treatment. Traditional therapies for syncope have included fludrocortisone and sodium chloride supplementation, alpha\(_2\) adrenergic agonists, and beta-adrenergic blocking agents.

**Fludrocortisone**

Fludrocortisone is a synthetic steroid with potent mineralocorticoid properties and high glucocorticoid activity.\(^6\) Mineralocorticoids increase reabsorption of sodium in the distal tubule of the nephron, resulting in fluid retention and an increase in blood pressure. Fludrocortisone may also increase peripheral alpha-adrenergic sensitivity, facilitating vasoconstriction. Low-dose fludrocortisone therapy, along with increased salt intake, has been used in the management of orthostatic intolerance for several decades.

In adolescents and adults, the usual fludrocortisone dose is 0.1-0.2 mg/day. Doses of 0.05-0.1 mg/day have been used for younger children. Fludrocortisone is available in 0.1 mg scored tablets. As a result of its long biologic half-life, 18 to 36 hours in adults, it can be given once daily. Full effects may not be seen for 2 to 3 weeks after beginning treatment. As with any long-term steroid use, fludrocortisone should be gradually tapered prior to discontinuation. The dose should be increased during periods of severe illness, trauma, or surgery to prevent drug-induced adrenal insufficiency. Patients receiving fludrocortisone should be monitored for steroid-related adverse effects as well as hypokalemia and encouraged to increase dietary potassium intake if necessary.\(^6\)

The utility of fludrocortisone in preventing recurrent syncope continues to be debated. While many clinicians have found it beneficial, there is little research to support its use. In 2005, Salim and Di Sessa randomized 33 children with a history of syncope and a positive tilt test to receive either fludrocortisone 0.1 mg/day and table salt 1 gram/day or placebo for one year.\(^7\) The average number of syncopal episodes prior to the study was 4.4 ± 4.8. Thirty-two children (mean age 13.9 ± 2.5 years, 20 females) were available at follow-up. Therapy was continued for an average of 176 ± 117 days. Syncopal episodes continued to occur in 10 of 18 children.
(55%) in the treatment group and 5 of 14 (36%) of the controls (p < 0.05). Patients in both groups experienced an increase in their symptoms after treatment was discontinued, suggesting a significant placebo response.

The impact of fludrocortisone on nausea associated with orthostatic intolerance was evaluated in 17 adolescents (11-17 years of age). All patients had a history of nausea, dizziness, or syncope and a confirmed diagnosis of orthostatic hypotension by tilt table testing. Fludrocortisone was given at a dose of 0.1-0.2 mg/day for a minimum of 4 weeks prior to assessment. The median duration of treatment was 11 weeks (range 4-54 weeks). At 4-week follow-up, 11 patients (65%) had significant improvement, defined as a reduction in nausea severity of more than 50%. One patient (6%) had moderate improvement, one (6%) had mild improvement, and the remaining four patients (24%) had no improvement. The effect of treatment on syncope was not reported. The authors concluded that fludrocortisone treatment appears to improve nausea associated with autonomic-mediated orthostatic intolerance.

**Midodrine**

Midodrine is a prodrug that forms an active metabolite, desglymidodrine, which functions as an alpha<sub>1</sub>-agonist. Desglymidodrine produces an increase in peripheral vascular resistance and reduces venous pooling when standing. In addition to this direct effect on the vessel wall, it may also provide an indirect increase in norepinephrine concentrations. Midodrine is commonly used in the treatment of orthostatic intolerance and may be used in combination with fludrocortisone and salt supplementation. Since desglymidodrine has a half-life of only 3 to 4 hours in adults, midodrine is typically given two to three times daily. It is available in 2.5 mg, 5 mg, and 10 mg scored tablets. The recommended dose in adults is 10 mg three times daily. Treatment for children with orthostatic intolerance is typically initiated at 2.5 mg once or twice daily, with subsequent titration based on patient response.

All patients receiving midodrine should be monitored for supine hypertension, with dose reduction or discontinuation of therapy in patients with a clinically significant increase in supine blood pressure. Midodrine is contraindicated in patients with renal or cardiac disease, pheochromocytoma, or thyrotoxicosis. Patients should be aware of the need to avoid over-the-counter cough and cold products that may produce additive effects on blood pressure while taking midodrine. Since neither midodrine nor desglymidodrine cross the blood brain barrier, there is minimal risk for the adverse central nervous system effects seen with other alpha<sub>1</sub>-adrenergic agonists, however, midodrine has been associated with nausea, abdominal discomfort, and headache in some patients.

A group of investigators from the Department of Pediatrics at Peking University First Hospital have conducted a series of studies with midodrine in children with POTS. In 2011, Chen and colleagues compared midodrine to metoprolol in children with POTS. Fifty-three children (mean age 12.2 ± 2.4 years, range 6-17 years) were randomized to receive midodrine 2.5 mg once daily plus conventional therapy (group 1), metoprolol 0.25 mg/kg twice daily plus conventional therapy (group 2), or conventional therapy alone (group 3). Conventional therapy consisted of increased water and salt intake, counter measures, and avoidance of triggers. Patients were scored according to their symptoms of orthostatic intolerance: syncope, dizziness, chest pain, nausea, palpitations, headache, or blurred vision. Scores ranged from 0 (no symptoms) to 4 (more than one episode of one or more symptoms during a single day). Symptom scores were assessed at baseline and 3-6 months after treatment. Cure was defined as being symptom-free. A reduction in score of 50% or greater was considered improvement, while a reduction of less than 50% was considered inefficacy.

Symptom scores in group 1 were significantly lower than groups 2 and 3 at follow-up (1.1 ± 2.2 versus 2.8 ± 2.4 and 3.7 ± 2.0, p < 0.05). The percentage of patients with a clinical cure or improvement were significantly higher in group 1 compared to groups 2 and 3 (68.42% versus 42.11% and 20.00%, respectively, and 89.476% versus 57.89% and 53.33%, all p < 0.05). There was no significant difference between groups 2 and 3. At long-term follow-up (mean 15.0 ± 4.3 months, range 5-24 months), the rate of symptom recurrence was significantly lower in group 1 compared to groups 2 and 3 (p < 0.05). There was no difference between groups 2 and 3. Systolic blood pressure increased in three of the children taking midodrine. The average increase was 5 mmHg, and none of the children were symptomatic. One child taking midodrine experienced nausea and vomiting, but none of the study patients discontinued treatment because of adverse effects.

Three other papers from the group have focused on markers to predict response to midodrine in children with POTS. In 2012, Zhang and colleagues suggested that the response to midodrine may be predicted by measurement of the midregional fragment of pro-adrenomedullin (MR-proADM). This compound is produced in equimolar amounts to adrenomedullin (ADM), a
circulating vasopeptide with potent vasodilator effects known to be elevated in POTS, and can serve as a surrogate marker for the more quickly degraded ADM. Levels of MR-proADM were evaluated in 57 children with POTS (mean age 11 ± 3 years) treated with midodrine and a control group of 20 healthy children (10 ± 3 years). Forty-four of the children with POTS were treated with midodrine 2.5 mg/day. The mean symptom scores pre- and post-treatment in these children were 5.6 ± 2.6 and 2.9 ± 2.7, p < 0.001. Twenty-seven children were classified as responders (defined as a reduction in symptom score of 2 or greater at 3 months), while 17 were classified as non-responders. Mean post-treatment symptom scores were 1.3 ± 1.3 and 5.5 ± 2.4 in the responders and non-responders, respectively (p < 0.01).

At baseline, the children with POTS had significantly higher levels of MR-proADM than the controls (75.0 pg/mL versus 58.5 pg/mL, p < 0.01). Among the children with POTS who were treated with midodrine, baseline levels of MR-proADM were significantly higher in the responders than in the non-responders (76.0 pg/mL versus 59.0 pg/mL, p < 0.01). Using a level ≥ 61.5 pg/mL as the cut-off, MR-proADM had a sensitivity of 100% and specificity of 71.6% in predicting response to midodrine in children with POTS, suggesting that it may be a useful test in this setting.

These investigators have also evaluated flow-mediated vasodilation (FMD) as a predictor of midodrine response. A total of 108 children with POTS (12 ± 3 years of age) and 20 healthy age-matched controls were enrolled into this prospective study. The mean symptom score at baseline in the children with POTS was 4.0 ± 2.2. All of the children with POTS were treated with midodrine 2.5 mg/day. Measurement of FMD was made using color Doppler ultrasound of the brachial artery according to recommendations from the American College of Cardiology. Baseline FMD values and the increase in heart rate during tilt table testing were significantly greater in the children with POTS compared to the controls: FMD 11.0 ± 3.3% versus 5.6 ± 2.2% and heart rate change 38 ± 9 bpm versus 7 ± 7 bpm (p < 0.001).

Ninety of the children with POTS (83%) responded to midodrine. FMD values, heart rate during tilt table testing, and symptom scores were significantly reduced in these patients after treatment. Mean symptom scores declined in the responders from 4.1 ± 2.3 to 0.5 ± 1.0 at 1 month and 0.4 ± 0.9 at 3 months, compared to the non-responders with scores of 3.8 ± 1.7 at baseline, 3.0 ± 1.8 at 1 month and 2.9 ± 1.6 at 3 months (p < 0.05). Responders had significantly higher FMD values than non-responders at baseline, (12 ± 3% versus 9 ± 2%, p < 0.05). Using an FMD cut-off value of 9.85%, the authors estimate a sensitivity of 74.4% and specificity of 77.8% for FMD testing to predict the response to midodrine.

In 2013, Deng and colleagues investigated the value of the change in blood pressure from supine to standing positions in predicting response to midodrine in children with POTS. The authors were interested in finding a less expensive and time-consuming tool than MR-proADM and FMD studies while maintaining a similar degree of sensitivity and specificity. A total of 110 children with POTS were included. After baseline testing, all patients were treated with midodrine 2.5 mg/day. A total of 104 children were available for follow-up at 6 months. Response to therapy was determined by reduction in symptom scores, as in the groups’ earlier studies. Efficacy was defined by a symptom score that decreased by 2 or more from baseline. A receiver operating characteristic (ROC) curve analysis was conducted to determine the probability of using systolic blood pressure (SBP) or diastolic blood pressure (DBP) changes as a predictor of response to treatment.

The pre-treatment increase in blood pressure upon rising from a supine position was significantly lower in midodrine responders than in the non-responders. (delta SBP 0.3 ± 6.9 mmHg versus 6.2 ± 10.7 mmHg and delta DBP 3.8 ± 8.5 mmHg versus 12.9 ± 7.0 mmHg, p < 0.01). The ROC curve suggested that midodrine would be effective when the pre-treatment increase in SBP from supine to standing positions was ≤ 0 mmHg or when the increase in DBP was ≤ 6.5 mmHg, with a sensitivity of 72% and specificity of 88%. Using these parameters, the change in blood pressure from lying to standing appears to be a quick and inexpensive tool for predicting response to midodrine in children with POTS.

The most recent publication on the use of midodrine in orthostatic intolerance was a double-blind, placebo-controlled cross-over study conducted in 20 patients between 12 and 20 years of age. The authors enrolled patients with both neuropathic (autonomic) POTS and hyperadrenergic postural tachycardia syndrome. Patients were randomized to 2 weeks of either midodrine 2.5-10 mg three times daily or placebo. After a 1 week wash-out at the completion of the first phase, the patients received the other treatment. In the patients with neuropathic POTS, midodrine produced a decrease in heart rate, calf blood flow, and calf venous capacitance during head up testing (supine to standing assessments), with increases
in mean arterial pressure and calf vascular resistance compared to placebo. In patients with hyperadrenergic postural tachycardia, there were no significant differences in response between midodrine and placebo. The authors concluded that midodrine was effective for orthostatic intolerance of neuropathic origin, but not in patients with a hyperadrenergic cause.

**Beta-adrenergic Blocking Agents**

Although early studies of beta-adrenergic blocking agents suggested an improvement in symptoms in patients with orthostatic intolerance, more recent studies have shown no benefit compared to placebo. In 2006, the Prevention of Syncope Trial showed no difference between metoprolol and placebo in preventing recurrent vasovagal syncope in adults. Subsequent studies with propranolol and metoprolol have confirmed these findings in both children and young adults. Based on the lack of demonstrated efficacy and the potential for adverse effects with this therapeutic class, beta-adrenergic blocking agents are no longer recommended for vasovagal syncope, POTS, or orthostatic hypotension.

**Summary**

Syncope is a relatively common occurrence in children and adolescents. While most patients don’t require treatment, those with syncope related to autonomic-mediated orthostatic intolerance, particularly POTS or orthostatic hypotension, may benefit from pharmacologic treatment. Fludrocortisone, in conjunction with increased sodium intake, and midodrine may reduce symptoms and improve quality of life, but not all patients respond to treatment. Recent studies have identified several methods to predict responsiveness to midodrine and may facilitate the development of treatment plans for children and adolescents with POTS or orthostatic hypotension.

The editors would like to thank Dr. Nancy McDaniel for serving as our guest editor for this issue of the newsletter.

**References**


**Formulary Update**

The following actions by the Pharmacy and Therapeutics Committee at their March 2014 meeting:

1. Supersaturated calcium phosphate rinse (Caphosol®) was added to the Formulary.
2. Eculizumab (Soliris®) was added with restriction to FDA-approved indications with Hematology approval.
3. Obinutuzumab (Gazyva™) was added with restriction to FDA-approved indications.