Midodrine in Neurally Mediated Syncope: A Double-Blind, Randomized, Crossover Study

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Neurally mediated syncope is the most frequent cause of syncope in patients without structural heart disease. Its most common trigger is a reduction in venous return to the heart due to excessive venous pooling in the legs. We conducted a double-blind, randomized, crossover trial to investigate the efficacy of midodrine, a selective α-1 adrenergic agonist that decreases venous capacitance, in preventing neurally mediated syncope triggered by passive head-up tilt. Twelve patients with history of recurrent neurally mediated syncope, which was reproduced during head-up tilt, were randomized to receive a nonpressor dose of midodrine (5mg) or placebo on day 1 and the opposite on day 3. One hour after drug or placebo administration, patients underwent 60-degree head-up tilt lasting 40 minutes (unless hypotension or bradycardia developed first). In the supine position, midodrine produced no significant change in blood pressure or heart rate. The responses to head-up tilt were significantly different on the midodrine and the placebo day: on the placebo day, 67% (8/12) of the subjects suffered neurally mediated syncope, whereas only 17% (2/12) of the subjects developed neurally mediated syncope on the midodrine day ($p < 0.02$). These results indicate that midodrine significantly improves orthostatic tolerance during head-up tilt in patients with recurrent neurally mediated syncope.

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Neurally mediated syncope is the most frequent cause of syncope in patients without structural heart disease. It is believed that the most common trigger of neurally mediated syncope is a reduction in cardiac venous return due to excessive venous pooling in the legs, particularly when intravascular volume is reduced. In some individuals, however, neurally mediated syncope occurs with no apparent trigger.[1] Regardless of the trigger and for unclear reasons, the normal autonomic efferent pattern that maintains orthostatic blood pressure is reversed in neurally mediated syncope with sympathetic vasoconstrictor outflow decreasing (producing vasodilatation) and parasympathetic outflow increasing (slowing the heart rate).[2]

Neurally mediated syncope is generally a benign problem, but in certain patients it can be a recurrent event and lead to bone fractures and head trauma. Although a variety of agents have been used to treat neurally mediated syncope, there is still no effective therapy. We postulated that an α-adrenergic agonist might be effective in preventing neurally mediated syncope by both increasing peripheral vascular resistance and reducing blood pooling in the legs during orthostatic stress. Of the α adrenergic agents, midodrine, a selective α-1 adrenergic agonist, is particularly attractive because it significantly decreases venous capacitance and may be effective at doses that do not increase blood pressure. Furthermore, midodrine does not cross the blood–brain barrier and thus has no central nervous system side effects. Here, we report the results of a double-blind, randomized, crossover trial to investigate the efficacy of a dose of midodrine without pressor effect, in preventing neurally mediated syncope triggered by passive head-up tilt in patients with history of recurrent spontaneous syncope.

Patients and Methods

Patients

The study included 12 patients (2 men, 10 women; age, 42 ± 4 years [mean ± standard error]) with a history of at least two syncopal episodes during the previous year (ranging from 2 to >15 episodes), reproduced during a drug-free tilt table test and thus confirmed as neurally mediated (ie, acute hypotension and absolute or relative bradycardia with symptoms of cerebral hypoperfusion).

Study Protocol

This was an outpatient, double-blind, randomized, crossover, placebo-controlled trial (Fig 1). The sponsor of the study, Shire Pharmaceutical Development, Inc., (Rockville, MD), supplied midodrine but did not design the study, collect, analyze, or interpret the data and did not write any part of this report. The study lasted 3 days. Subjects were instructed to avoid caffeine-containing food and abstain from cigarette smoking for 24 hours before the study and to fast for 8

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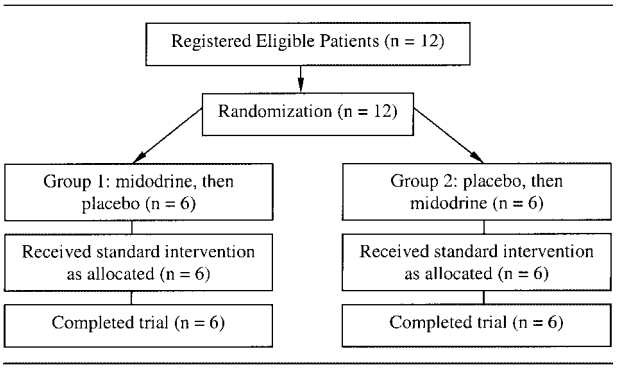

Fig 1. Profile of randomized trial.

hours. After signing informed consent approved by the Institutional Review Board of the Mount Sinai School of Medicine, patients were assigned by restricted randomization technique into crossover Group 1 (midodrine on day 1, placebo on day 3) or Group 2 (placebo on day 1, midodrine on day 3). Day 2 was a washout day. Allocation schedule was performed by a study coordinator, not familiar with the patients, on the basis of a computer-generated random number sequence. The coordinator kept the allocation information in the sealed envelope, and the randomization file was deleted. Midodrine and placebo were supplied by Roberts Pharmaceuticals and kept by the study coordinator. No events during this trial required breaking the code. Patients and physicians were blinded throughout the study to the order of treatment assignment. Four patients, however, described having itching sensation on the skin on one of the medication days, and three of them specifically mentioned itching of the scalp; therefore, the complete blindness of the patients to administered medication cannot be ascertained.

Baseline evaluation consisted of noninvasive autonomic reflex testing, 12-lead electrocardiogram, complete blood count, and blood chemistry. Patients received 5mg of midodrine or placebo at 9:00 AM and underwent a passive 60-degree head-up tilt test 1 hour later. Blood pressure (Finapres; Ohmeda, Englewood, CO) and heart rate (HP 78352 A; Hewlett-Packard, GMBH, Boeblingen, Germany) were continuously monitored via an ASYST data acquisition system (Asyst Technologies, Fremont, CA). Tilt lasted 40 minutes unless hypotension, bradycardia, or symptoms of cerebral hypoperfusion developed, in which case patients immediately were returned to the horizontal position.

Statistical Analysis

The primary analysis of the data was an intention-to-treat analysis comparing the effect of midodrine on the course and the outcome of the head-up tilt test. The primary variables were the blood pressure and heart rate (supine, during head-up tilt at 1, 3, and 5 minutes, and at the moment of the lowest systolic pressure) and the occurrence and time of syncopal or near syncopal episode, if applicable. Repeated-measures analyses of variance (with medication and body position as within-subject factors) were used to compare the blood pressure and heart rate data while supine and at 1, 3, and 5 minutes during head-up tilt. The blood pressure and heart rate data at the moment of lowest systolic blood pressure during head-up tilt were compared between trials using paired samples t tests and between groups of fainting and nonfainting patients by using independent measures t tests. Orthostatic tolerance during head-up tilt was compared between the treatment conditions using the Fisher's exact test. Test results with probability values less than 0.05 were considered significant.

Results

All enrolled patients completed the study protocol. Noninvasive autonomic testing including respiratory sinus arrhythmia and Valsalva maneuver were normal in all patients.

As shown in the Table, midodrine induced no significant changes in blood pressure or heart rate in the supine position. On the placebo day, the average systolic blood pressure decreased significantly during the orthostatic stress of head-up tilt (from 123 ± 4 to 94 ± 9mm Hg, δ 30 ± 9mm Hg, mean ± standard error; $p < 0.05$), whereas on the midodrine day the average systolic blood pressure did not change significantly (from 122 ± 4 to 116 ± 6mm Hg, δ 7 ± 7mm Hg; p = not significant). Moreover, during the day patients received midodrine, only two (17%) experienced syncope during head-up tilt, whereas on the day they received placebo, eight (67%) developed syncope ($p < 0.02$).

As expected, when patients suffered syncopal episodes they had significant bradycardia during both midodrine (from 83 ± 8 to 57 ± 7 beats per minute [bpm]; $p < 0.05$) and placebo treatments (from 99 ± 4 to 64 ± 5 bpm; $p < 0.0001$; Fig 2). In the absence of syncope, after placebo administration, heart rate at the time of lowest systolic blood pressure during head-up tilt had a tendency to be lower (71 ± 5 bpm) than after midodrine treatment (80 ± 5 bpm), although the difference did not reach statistical significance ($p = 0.08$).

Because it has been suggested that the frequency of tilt-induced syncope decreases with repeated tilt regardless of treatment, we analyzed whether the order in which patients received medication altered the outcome. Of the eight patients who fainted on placebo, four received placebo first and four received midodrine first. Thus, the order of randomization made no difference in the outcome.

The Kaplan–Meier curves show orthostatic tolerance during head-up tilt on each day (Fig 3). On the midodrine day, all but two patients (83%) remained symptom free for 40 minutes. On the day that they received placebo, there was a progressive decline in the number of patients who tolerated the upright position, but the average time at which syncope occurred after midodrine or placebo administration was similar (15 ± 1 vs 24 ± 4 minutes, $p = 0.28$).

Table. Blood Pressure and Heart Rate in the Supine Position and during Head-Up Tilt after Midodrine and Placebo (mean ± SE)

	Midodrine			Placebo		
Position (min)	SBP (mm Hg)	DBP (mm Hg)	HR (bpm)	SBP (mm Hg)	DBP (mm Hg)	HR (bpm)
Supine	122 ± 4	71 ± 3	65 ± 2	123 ± 4	69 ± 3	69 ± 3
HUT (1)	133 ± 5	84 ± 2	69 ± 3	134 ± 5	83 ± 4	74 ± 3
HUT (3)	137 ± 3	87 ± 2	73 ± 3	131 ± 4	84 ± 3	78 ± 2
HUT (5)	135 ± 3	86 ± 2	74 ± 3	131 ± 4	84 ± 3	78 ± 3
Lowest SBP	116 ± 6	80 ± 5	81 ± 5	94 ± 9[a]	61 ± 6	71 ± 5

[a] $p < 0.05$ (midodrine vs placebo).

SBP = systolic blood pressure; DBP = diastolic blood pressure; HR = heart rate bpm = beats per minute; HUT = head-up tilt.

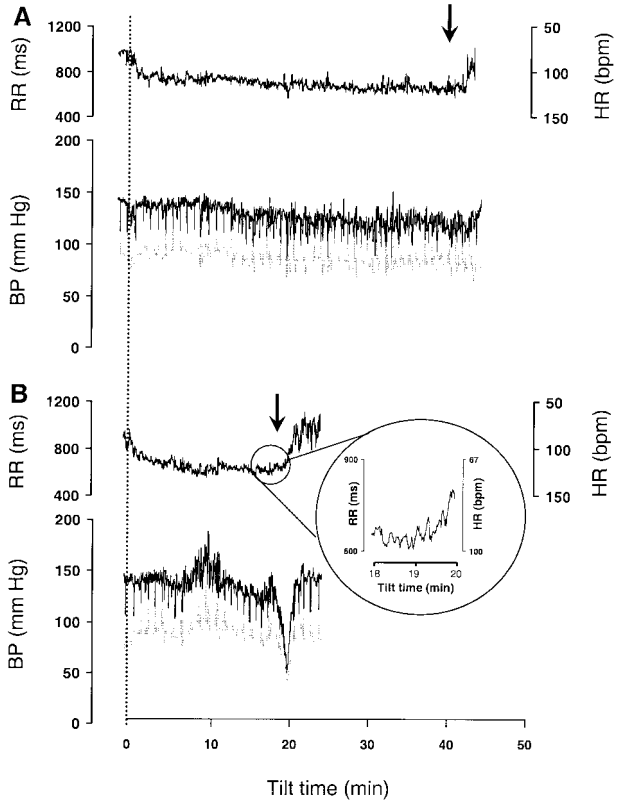

Fig 2. Electrocardiograph RR intervals (left), heart rate (right), and systolic/diastolic blood pressure (bottom) in Patient 4 1 hour after midodrine (A) or placebo (B) administration. Dotted line indicates time of head-up tilt; arrow indicates time of tilting down. Inset in B shows RR interval and heart rate at the time of the acute blood pressure decrease and syncope. BP = blood pressure; HR = heart rate; bpm = beats per minute; ms = millisecond.

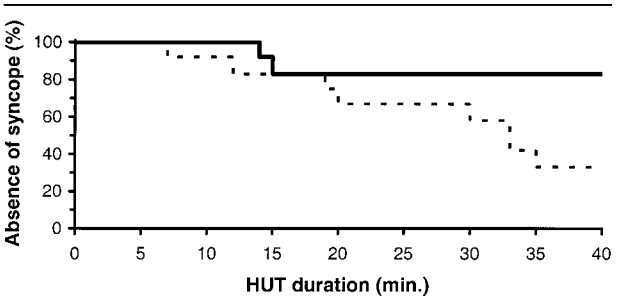

Fig 3. Kaplan–Meier plot. Effect of midodrine (solid line) *and placebo* (dashed line) *on orthostatic tolerance during head-up tilt (HUT).*

Discussion

The results of this study show that a dose of the α agonist midodrine that produced no change in blood pressure or heart rate in the supine position significantly improved orthostatic tolerance in patients with recurrent, reproducible neurally mediated syncope. Eighty-three percent of subjects tolerated a 40-minute passive head-up tilt after administration of 5mg of midodrine, whereas only 33% tolerated prolonged tilt after receiving placebo. In a previous study,[3] midodrine also proved effective in reducing upright tilt-induced syncope, but patients were older (age, 56 ± 4.5 vs 42 ± 4 years, mean ± SE; $p < 0.05$) and had received midodrine 5mg three times per day for a month, which significantly increased the systolic blood pressure in the supine position.

The mechanism by which midodrine improved orthostatic tolerance cannot be ascertained by this study. Because supine blood pressure did not increase in our study, it is unlikely that the effectiveness of midodrine was because of arterial vasoconstriction. Midodrine reduces venous capacitance,[4] and thus it is likely that it may have reduced pooling of blood in the lower part of the body during head-up tilt, as shown by Ward and colleagues,[3] thereby preventing the trigger of neurally mediated syncope. Indeed, midodrine has been found to be effective in reducing post–bed rest orthostatic intolerance, a condition that may be caused by excessive blood pooling in the legs.[5]

Regardless of the mechanism of action, the attractiveness of midodrine as a potential therapy is not only because of its effectiveness at nonpressor doses, but also because it does not cross the blood–brain barrier and

therefore does not have side effects such as anxiety, agitation, and insomnia common with other α agonists.

Several other pharmacological agents have been attempted to prevent neurally mediated syncope including fludrocortisone, β-blockers, serotonin reuptake blockers, antiarrhythmics, and α agonists. Fludrocortisone with increased salt intake is effective by producing volume expansion, but the long-term effects of this treatment particularly mineralocorticoid-induced hypertension[6] are of concern. Although β-blockers are widely used, a recent prospective, double-blind, randomized and placebo-controlled study[7] showed lack of efficacy for atenolol. Similarly, disopyramide appeared effective in small trials but was not better than placebo in a double-blind crossover trial.[8] The serotonin reuptake inhibitor paroxetine showed effectiveness in a double-blind trial,[9] but side effects with this agent are common. A recent multicenter, randomized, placebo-controlled study evaluating the α agonist etilefrine, which has both central and peripheral α-adrenergic effects, failed to show effectiveness in the long-term management of patients with recurrent neurally mediated syncope.[10]

Although our study suggests that midodrine may be effective in neurally mediated syncope, the results of acute tilt testing may not predict the long-term efficacy of therapeutic interventions for spontaneous syncope.[11] In addition, whether long-term treatment is advisable in patients with occasional syncope is arguable, and the possibility of using a low-dose vasoconstrictor such as midodrine only before situations known to trigger neurally mediated syncope may be reasonable.

In summary, midodrine significantly improved orthostatic tolerance 1 hour after administration in subjects with recurrent neurally mediated syncope. The effect of chronic midodrine administration to prevent neurally mediated syncope, or alternatively using it "on demand" before situations known to trigger syncope should be assessed.

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