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Pharmacotherapy of Neurally Mediated Syncope

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Abstract—A wide variety of pharmacological agents are currently used for prevention of recurrent neurally mediated syncope, especially the vasovagal faint. None, however, have unequivocally proven long-term effectiveness based on adequate randomized clinical trials. At the present time, β-adrenergic receptor blockade, along with agents that increase central volume (eg, fludrocortisone, electrolyte-containing beverages), appear to be favored treatment options. The antiarrhythmic agent disopyramide and various serotonin reuptake blockers have also been reported to be beneficial. Finally, vasoconstrictor agents such as midodrine offer promise and remain the subject of clinical study. Ultimately, though, detailed study of the pathophysiology of these syncopal disorders and more aggressive pursuit of carefully designed placebo-controlled treatment studies are essential if pharmacological prevention of recurrent neurally mediated syncope is to be placed on a firm foundation. **(*Circulation*. 1999;100:1242-1248.)**

Key Words: syncope ■ nervous system ■ pharmacology ■ Cardiovascular Drugs

Neurally mediated (neurocardiogenic) syncope comprises a number of clinical conditions in which symptomatic systemic hypotension occurs as a result of a transient disturbance of neural reflex cardiovascular control (Table 1).[1–3] The vasovagal faint, carotid sinus syndrome, and postmicturition syncope are the most common forms of the neurally mediated faint. Others, including cough syncope and postexertional syncope, are less frequently encountered.

This communication focuses on the pharmacological options that have been proposed for preventing neurally mediated faints, and especially the vasovagal faint, because it has been the most thoroughly studied. The objective is to provide an overview of the pharmacology and pertinent proposed modes of action of those agents that may be of benefit.

Drug Therapy of Neurally Mediated Syncope: Basic Principles

Most individuals who experience a neurally mediated faint (particularly vasovagal fainters) require no additional therapy beyond education (ie, recognition of premonitory symptoms, avoidance of triggering events, and awareness of useful evasive actions) and reassurance regarding the non–life-threatening nature of the condition. On occasion, stress and anxiety management may be warranted. Various more aggressive nonpharmacological (eg, support hose, extended exposure to upright posture, pacemakers) and pharmacological treatment options are usually reserved for those relatively few individuals who experience frequent syncope and/or when symptoms cause excessive lifestyle difficulties, threaten employment, or result in unacceptable risk of physical injury to the patient or others.

Currently, drugs are used for both diagnostic and therapeutic purposes in the patient with neurally mediated syncope.[1–3] In terms of diagnostic applications, agents such as isoproterenol, edrophonium, nitroglycerin, and adenosine have been reported to be helpful during tilt-table testing (ie, so-called pharmacological provocation technique).[4–8] ATP and adenosine have also been found to unmask susceptibility to neurally mediated paroxysmal AV block, one of the important electrocardiographic manifestations of cardioinhibitory neurally mediated syncope.[9,10] In regard to treatment, drugs may be used for both emergent resuscitation of severely hypotensive and bradycardic victims (eg, dopamine, norepinephrine, anticholinergics), as well as for long-term prevention of syncope recurrences. The resuscitation role is a relatively rare occurrence, being perhaps most often encountered during the course of an acute inferior wall myocardial infarction complicated by triggering of the Bezold-Jarisch reflex. Long-term prophylaxis is a much more common issue; however, drug efficacy in this setting remains controversial, and certain important caveats need to be noted. First, to date, all evidence supporting the utility of prophylactic pharmacological interventions in vasovagal syncope is undermined by absence of large-scale randomized controlled treatment trials. Virtually all existing published reports are uncontrolled. Second, for most of the proposed treatments, the overall published experience is small and retrospective. Finally, the study end points have often been unrealistic. Specifically, it is unlikely that any tolerable intervention will entirely eliminate all events (a situation comparable, for example, to current treatment of paroxysmal atrial fibrillation). Moreover, because symptoms may wax and wane in frequency over many months, it is often difficult to assess the efficacy of any intervention. Conse-

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TABLE 1. Neurally Mediated Syncopal Syndromes

Vasovagal syncope (common or emotional faint)
Carotid sinus syncope
Postmicturition syncope
Airway stimulation
Cough syncope
Sneeze syncope
Gastrointestinal stimulation
Swallow syncope, defecation syncope
Raised intrathoracic pressure
Trumpet playing, weight lifting
Glossopharyngeal neuralgia
Miscellaneous
Syncope associated with aortic stenosis
Syncope accompanying onset of certain tachyarrhythmias (atrial fibrillation, paroxysmal supraventricular tachycardia, and possibly certain episodes of ventricular tachycardia)

quently, clinical studies must of necessity focus on more practicable end points: the severity (ie, syncope versus near syncope) and frequency (ie, syncope burden) of episodes, the time to first recurrence, the duration of symptom-free intervals, the presence or absence of a premonitory warning, and the occurrence of physical injury or accident. The recently reported North American Vasovagal Pacemaker Study[11–13] provides an example of how this can be done.

In broad terms, drugs used for preventing neurally mediated syncope recurrences comprise 2 principal categories: (1) agents used to ameliorate an underlying disease state known to trigger faints in a given individual or (2) drugs used in an attempt to modify the neural reflex disturbance directly and thereby diminish susceptibility to recurrent events. The first category is exceedingly diverse and may include, for example, agents used to treat exacerbations of pulmonary disease for patients with cough syncope or analgesic agents in patients with periodic faint-inducing pain syndromes. The second category (ie, drugs addressing the reflex arc at $\geq$1 sites) includes β-adrenergic blockers, disopyramide, certain vasoconstrictors (eg, etilephrine, midodrine), serotonin reuptake inhibitors, and volume retention agents (eg, fludrocortisone). This second group forms the focus of this report.

Specific Pharmacological Agents

β-Adrenergic Receptor Blocking Drugs

β-Adrenergic receptor blocking drugs were among the first agents proposed for prevention of vasovagal syncope,[4] and they remain widely used for this purpose. They are a logical choice, because both spontaneous and tilt-table–induced faints are often presaged by elevated levels of circulating epinephrine.[3,4,14–16] It is thought that epinephrine increases the sensitivity of various mechanosensitive and/or chemosensitive trigger sites, the presumed source of the afferent neural reflex signals. Epinephrine may also enhance responsiveness to the efferent parasympathetic activity associated with these syndromes ("accentuated antagonism").[17,18] Finally, the β-adrenergic action of epinephrine may facilitate peripheral vasodilatation.

β-Adrenergic blocking drugs have been evaluated during both acute intravenous drug administration and longer-term oral use in vasovagal fainters. For example, Asso et al[19] observed that in a cohort of 21 consecutive patients followed up for at least 3 years, 11 exhibited conversion of a positive tilt-table response to a negative response after parenteral administration of metoprolol (10 mg). During follow-up, only 1 of these metoprolol responders had a clear-cut syncopal episode. Metoprolol nonresponders were treated with alternative agents, and consequently the value of a tilt-test "failure" for predicting ineffective therapy was not evaluated. The latter question, however, was addressed in a study by Muller et al.[20] In this report, metoprolol proved effective in preventing recurrences of syncope over a 10-month follow-up period in 7 of 12 patients who had had a negative tilt response after administration of intravenous metoprolol but also in 2 of 3 patients who had remained tilt-positive after parenteral drug. Muller et al suggested that the apparent discordance between apparent failure during acute testing and subsequent long-term "success" may be attributable to pharmacokinetic factors. Parenteral metoprolol is lipid soluble and has a large volume of distribution. Therefore, the adequacy of tissue concentrations may be an issue after acute administration, with the preponderance of drug going to tissues with high blood flow and lipid content. Conversely, oral metoprolol undergoes a hepatic "first-pass" effect, which may lead to interindividual differences during oral treatment. Others argue that the findings simply point to the inadequacy of tilt-table testing for predicting treatment outcomes and/or the ineffectiveness of β-adrenergic blockade in this setting. However, in contrast to the above-noted findings with parenteral metoprolol, Sra et al[21] found a strong concordance between the effects of intravenous esmolol during tilt-testing and subsequent β-adrenergic blocker efficacy. In their report, esmolol eliminated susceptibility to tilt-induced syncope in 17 of 27 tilt-table–positive syncope patients, and in all 17 cases, subsequent oral β-adrenergic blockade therapy with metoprolol was effective. They suggest that because esmolol administration is associated with stable plasma concentrations within 4 minutes and a rapid dose-dependent β-adrenergic blockade is achieved and maintained, it provides a more consistent patient-to-patient β-adrenergic blocking effect after acute administration than does metoprolol.

Metoprolol, pindolol, and atenolol have been the most frequently studied β-adrenergic blockers in vasovagal syncope.[4,19–25] Metoprolol was the first β-blocker tested in tilt-induced syncope, on the bases of both its availability for parenteral testing in the United States and its relative cardioselectivity.[4] Pindolol has gained favor because of its intrinsic sympathomimetic activity, which diminishes the severity of resting bradycardia in treated patients.[22] Overall, there is as yet no compelling evidence to suggest that any β-adrenergic blocker is superior to others.

Disopyramide

Disopyramide is a class 1a antiarrhythmic agent with prominent vagolytic side effects and a disconcerting degree of

negative inotropic effect. The latter attribute caused considerable concern regarding the usefulness of the drug in many antiarrhythmic applications but was paradoxically beneficial in patients with obstructive cardiomyopathy.[26] On the basis of the latter observation, we proposed its use in preventing vasovagal syncope.[27] The rationale at the time was that agents that diminish cardiac contractility might reduce stretch on cardiac and other centrally located cardiovascular receptors (eg, aortic arch, pulmonary arteries) and thereby diminish afferent neural reflex traffic. In addition, the vagolytic action of disopyramide offered the opportunity for maintaining heart rate and possibly alleviating ancillary vagally mediated symptoms associated with vasovagal episodes. Potential adverse consequences included torsade de pointes ventricular tachycardia in patients prone to drug-induced QT interval prolongation, urinary tract obstruction in older patients, and glaucoma.

Disopyramide continues to be used in vasovagal syncope, although its utility has been questioned.[28] Among 21 patients followed up by Morillo et al[28] for an average of 30 months, syncope recurrence was comparable in both disopyramide- and placebo-treated groups (disopyramide, 27%; placebo, 30%). End points such as time to first recurrence or syncope burden were not reported. Other studies support the clinical utility of disopyramide phosphate.[27,29–31] The required dose of disopyramide, however, has been a source of controversy, with the range varying from 200 to >700 mg/d. In this regard, Kelly et al[29] pointed out that doses as high as 450 mg/d were ineffective in many of their patients and that the mean daily dose required for success was 700±219 mg in their 15 study patients. Additional placebo-controlled experience with disopyramide is needed. Currently, controversy regarding its effectiveness aside, disopyramide is best chosen for the young, active fainter without structural heart disease or QT-interval prolongation. In this setting, it may be more tolerable than a β-adrenergic blocker.

Serotonin Reuptake Blockers

Serotonin (5-hydroxytryptamine) is a neurotransmitter important in blood pressure regulation. Activation of cerebral serotonin receptors inhibits sympathetic nervous system activity and thereby facilitates a vasodepressor response.[32,33] Although little is known regarding serotonin levels during neurally mediated faints, 2 indirect lines of evidence suggest at least the possibility of a contributory role. First, intracerebroventricular serotonin administration has been reported to inhibit sympathetic neural outflow in general while simultaneously increasing adrenal sympathetic stimulation.[34–36] This finding could account for the combination of diminished peripheral vasoconstriction (reduced synaptic norepinephrine release) and concomitant excess epinephrine excretion known to occur in vasovagal fainters. Second, clinical observations suggest that serotonin reuptake blockers may diminish susceptibility to certain neurally mediated syncopal events.[32,37] Selective serotonin reuptake blockers reversibly block serotonin reuptake in the synaptic cleft, ultimately reducing the effects of serotonin on sympathetic neural activity and thereby possibly moderating vasodepressor tendencies in neurally mediated syncope. In this regard, an early uncontrolled report examined the effects of fluoxetine hydrochloride in 16 patients who had failed conventional pharmacological approaches (scopolamine, disopyramide, etc).[38] Thirteen of these 16 patients tolerated long-term therapy, and 7 (44%) remained syncope-free during 19±9 months of follow-up. Subsequently, the serotonin inhibitor sertraline hydrochloride was assessed in 17 patients[39]; 3 were intolerant of therapy, and 5 remained tilt-table positive. Of the remaining tilt-table–negative patients, all were reported to have remained asymptomatic during 12±5 months of follow-up. Finally, Grubb and Kosinski[39] suggest that the serotonin reuptake inhibitor verlafaxine hydrochloride may be even more effective. To date, however, all of these observations should be considered anecdotal.

Serotonin reuptake inhibitors may also be useful in forms of neurally mediated syncope other than vasovagal syncope. In carotid sinus syndrome, Grubb et al[40] observed apparently beneficial effects of sertraline in one case and fluoxetine in another. These observations, if confirmed, may be important because, with the possible exception of midodrine, there are as yet no other pharmacological agents to assist in treating patients with nonvasovagal neurally mediated syncope.

Midodrine and Other Vasoconstrictors

Drugs that promote vasoconstriction (or at least impede vasodilation associated with the vasodepressor component of neurally mediated syncope) are natural contenders for prophylactic treatment of the neurally mediated syncopal syndromes. In the past, ephedrine, dihydroergotamine, and etilephrine have been tried at various times.[39,41,42] However, drug-induced hypertension, tachyphylaxis, and inconsistent effectiveness have largely eliminated their use. For instance, a multicenter randomized placebo-controlled study examining the utility of etilephrine (a relatively weak α- and β-adrenergic agonist) in neurally mediated syncope was terminated after no apparent etilephrine benefit was observed.[42] Occurrence of syncope (etilephrine, 25.9%; control, 23.6%) and time to first syncope recurrence did not differ significantly between active drug–treated and placebo-treated patients. On the other hand, early experience with the recently introduced α_1-agonist midodrine has been encouraging in both orthostatic hypotension and neurally mediated syncope applications.[43–46]

Midodrine [1(2′,5′-dimethoxyphenyl)-2-glycinamido-ethanol-HCl] produces both arteriolar constriction and diminished venous pooling.[43,44] Midodrine is absorbed from the gastrointestinal tract and undergoes hepatic metabolism to an active metabolite, desglymidodrine. The latter reaches peak levels in ≈40 minutes and induces arteriolar and venous capacitance constriction. Elimination is via the urine. The duration of action is 4 to 6 hours, thereby requiring 3 to 4 daily doses. The initial starting dose is 2.5 mg 3 times daily, with the maximum dose being in the range of 40 mg/d. Neither midodrine nor its desglymidodrine metabolite crosses the blood-brain barrier. They have minimal cerebral and cardiac effects. Scalp tingling is perhaps the most common and annoying side effect with this otherwise generally well-tolerated agent.

The effects of midodrine have been studied in greatest detail in patients with neurogenic orthostatic hypotension. Gilden[43] reported observations of a dose-ranging placebo-controlled crossover trial in 97 individuals. An almost 30% average increase in standing systolic blood pressure was observed, with the dose of 10 mg 3 times daily seeming to be the most effective. More recently, Sra et al[45] provided findings in 11 patients (average age, 34 years) with recurrent vasovagal syncope whose symptoms had not been adequately controlled on conventional medications. One patient did not tolerate the drug because of headache and the development of hypertension despite a relatively low midodrine dose (7.5 mg/d). Among the remainder, 5 were symptom-free during the average 17-week follow-up, whereas 4 others reported symptom improvement compared with the 3-month baseline period just before they entered the trial. In our recent experience with 20 patients who had recurrent syncope over an average of >5 years despite multiple treatment regimens (average of 2.3 drugs), 13 remained completely asymptomatic after 14 months on midodrine therapy (average daily dose, 22 mg).[46]

Volume Maintenance

Maintenance of central volume is an underemphasized aspect of vasovagal syncope prevention, particularly in cases in which dehydration (eg, athletes) or extended periods of upright posture (eg, military) appear to play a role. In these circumstances, patients can be advised to liberalize their salt intake and use electrolyte-containing beverages (eg, sport drinks). The addition of fludrocortisone may also be beneficial. Fludrocortisone increases sodium and fluid retention and has been reported to sensitize α-adrenergic receptors (suggesting a possible synergism with midodrine). It is generally very well tolerated and is often used as a first choice in younger individuals without other cardiovascular disease.[39,47]

Other Clinical Pharmacological Avenues

Other pharmacological agents have been reported to be helpful, but for the most part, the evidence is very limited. One such drug is theophylline, a commonly used bronchodilator with adenosine receptor blocking action as well as an element of sympathomimetic activity. In this regard, long-acting theophylline preparations were proposed for treatment of certain young patients with neurally mediated symptomatic bradyarrhythmias.[48] A much more recent report describing the use of ATP and adenosine as provocative agents for identifying a subset of patients in whom paroxysmal AV block is a prominent manifestation of neurally mediated syncope has revived interest in theophylline and related adenosine A_1-receptor blockers.[9] As a rule, however, few patients with vasovagal syncope respond to theophylline alone.[49] The same may be said of scopolamine, which until recently was available for convenient administration by transcutaneous skin patch (usually applied every other day). Apart from inconsistent efficacy, scopolamine therapy tended to be associated with frequent troublesome anticholinergic side effects as well as tachyphylaxis. Consequently, it was never a popular treatment choice. Finally, 1 study reported methylphenidate to be beneficial, but the clinical experience is far too limited to warrant further comment.[39]

Potential Novel Pharmacological Approaches

Currently, our understanding of the factors that contribute to individual susceptibility to neurally mediated faints is very limited. Nevertheless, differences in neurohumoral and neuroreflex status appear to exist between individuals who are about to experience a vasovagal faint and those who are not. Examples of these include markedly elevated epinephrine, vasopressin, β-endorphins, and pancreatic polypeptide levels and altered baroreceptor sensitivity in the faint-prone individual.[50,51] Such differences (among many others of which we are as yet unaware) may impact the capability of the central nervous system to protect circulatory stability. In this regard, β-endorphin levels are increased in both vasovagal syncope and the analogous second stage of hemorrhagic shock.[52–54] The trigger for this increase and its precise timing are not known. However, as endorphin levels increase, their central action would be expected to accentuate efferent parasympathetic activity and possibly diminish efferent sympathetic activity. In an experimental hemorrhage model, intracisternal administration of the opioid receptor blocker naloxone was effective in preventing hypotension.[53] However, this effect was not demonstrable with peripheral naloxone administration during study of neurally mediated syncope in humans.[54] Possibly, then, endorphins may contribute to the evolving faint, and agents capable of blunting this effect may have therapeutic utility.

The possibility that nitric oxide may be a mediator in the vasodepressor response has been considered recently. Nitric oxide release from endothelial cells in the peripheral vasculature is known to contribute to smooth muscle relaxation. Nitric oxide is also known to play a role in the hypotension associated with sepsis. Experimental studies suggest that nitric oxide release may be a regulator of sympathetic neural tone,[55] and in addition, certain parasympathetic nerves terminating in the adventitia of large cerebral and retinal blood vessels are known to contain nitric oxide synthetase. Potentially, nitric oxide could play a role in the vasovagal faint if release from nerve endings results in both sympathetic neural inhibition and direct peripheral smooth muscle relaxation. In this regard, increased urinary cyclic 3′,5′-GMP (a presumed marker of nitric oxide activity) was reported during tilt-table testing.[56] Furthermore, nitric oxide activity has been associated with the forearm vascular dilatation accompanying mental stress.[57] On the other hand, Dietz et al[58] did not observe reversal of forearm vascular dilatation with the nitric oxide synthetase inhibitor N^G-monomethyl-L-arginine (L-NMMA). Similarly, findings suggesting that vasovagal syncope is accompanied by cerebrovascular spasm are not easily reconciled with the nitric oxide hypothesis, given the known nitric oxide synthetase activity in cerebral vessels.

Role of Tilt-Table Testing in Assessing Drug Therapy

It is generally agreed that head-up tilt-table testing is an important diagnostic aid in the evaluation of patients with recurrent syncope of unknown origin.[1,2,30,59–63] Conversely,

TABLE 2. Tilt-Table Testing for Predicting Effectiveness of Therapy

Reference	Tilt-Negative on Proposed Treatment	Follow-Up, mo	No Syncope During Follow-Up, %	Therapies
Grubb et al[30]	15	16	14 (93)	B-blk, Scop, Diso, Flcr
Sra et al[71]	34	18	32 (94)	B-blk, Diso
Grubb et al[67]	10	21±2	10 (100)	B-blk, Scop, Diso, Pacer
Sra et al[31]	19	16	18 (94)	B-blk, Diso, Theo
Milstein et al[27]	10	20±5	9 (90)	Diso
Raviele et al[66]	7	12 (9–16)	6 (86)	Etileph, Scop
Brignole et al[24]	15	11±7	7 (46)	B-blk, Ergot, others
Asso et al[19]	11	13 (1–36)	9 (82)	B-blk
Lurie et al[22]	17	19±0.9	16 (94)	B-blk
Grubb et al[70]	14	24±11	14 (100)	B-blk, Scop, Diso, B-blk+Flcr
Grubb et al[72]	17	23±7	17 (100)	Flcr, B-blk, Diso
Strieper et al[68]	16	11.7 (6–14)	15 (94)	Pseudoephedrine
Cox et al[69]	118	28±11	106 (90)	B-blk
Muller et al[20]	12	10	7 (58)	B-blk
Natale et al[62]	210	34±22	198 (94)	B-blk, Diso, Theo, Ephed
Total	525	18.5	478 (91)	

B-blk indicates β-adrenergic blockade; Scop, scopolamine; Diso, disopyramide; Flcr, fludrocortisone; Pacer, pacemaker; Theo, theophylline; Etileph, etilephrine; Ergot, ergotamine; and Ephed, ephedrine.

the value of tilt-table testing to qualify pharmacological agents for use in neurally mediated syncope patients or for predicting treatment efficacy in patients with neurally mediated vasovagal syncope is less certain. Table 2 summarizes findings from a number of published studies in which treatment for vasovagal syncope was based on findings during tilt-table testing studies but in which subsequent effectiveness was determined by clinical follow-up. In brief, ≈90% of patients in whom therapy resulted in a negative tilt study remained syncope-free during the observation period (mean, 18.5 months), a finding suggesting the utility of a tilt-table–guided approach. However, this outcome must be interpreted cautiously, given the absence of either placebo controls or a measure of the effect of empirical therapy in most studies. With regard to placebo control, the few available reports have usually failed to find benefit with current therapies.[24,28,42,47,64,65] To date, only atenolol has been shown to be effective in a randomized controlled trial.[25] The issue of the value of empirical treatment was addressed by Natale et al[62] in a retrospective nonrandomized analysis of clinical follow-up of 303 syncope patients in whom diagnostic tilt-table testing was positive. Three treatment subgroups were delineated: (1) 44 patients treated with empirical therapy, (2) 210 patients treated on the basis of therapy being effective during repeat tilt-table testing, and (3) 49 patients who refused or discontinued therapy. Treatment was heavily biased toward β-adrenergic blockers, both among those individuals in whom tilt-table testing was used to assess efficacy (130 of 210) and those receiving empirical treatment (37 of 44). During follow-up (2.8±1.8 years), symptom recurrences were less frequent ($P<0.001$) when tilt testing was used to assess efficacy (6%) compared with either empirical-treatment (36%) or no-treatment (67%) subgroups. The latter observation tends to support the utility of tilt-table testing for evaluating treatment options (particularly drugs), but larger prospective trials are still needed.

Conclusions

In conclusion, a wide variety of pharmacological agents are used to treat neurally mediated syncope. None, however, have unequivocally proven long-term effectiveness as shown by randomized clinical trials. Nevertheless, β-adrenergic receptor blockade and agents that increase central volume (eg, fludrocortisone, electrolyte-containing beverages), currently appear to be favored treatment options. Disopyramide and various serotonin reuptake blockers are also reported to be beneficial. Finally, vasoconstrictors such as midodrine offer promise, assuming that tachyphylaxis (a common problem with this class of drugs) does not hamper their continued effectiveness. Ultimately, however, more intensive study of the pathophysiology of these syncopal disorders and more aggressive pursuit of carefully designed placebo-controlled treatment studies are essential if pharmacological prevention of recurrent neurally mediated syncope is to be placed on a firm foundation.

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