Use of Sertraline Hydrochloride in the Treatment of Refractory Neurocardiogenic Syncope in Children and Adolescents

BLAIR P. GRUBB, MD, FACC, DANIELA SAMOIL, MD, DANIEL KOSINSKI, MD, KATRINKA KIP, MD, PAMELA BREWSTER, MA
Toledo, Ohio

Objectives. The purpose of our study was to determine whether the serotonin reuptake inhibitor sertraline hydrochloride could prevent neurocardiogenic syncope in children and adolescents resistant to or intolerant of other therapies.

Background. The serotonin reuptake inhibitor fluoxetine hydrochloride has been reported to be effective in preventing neurocardiogenic syncope in adults.

Methods. Seventeen consecutive young patients (mean age 15 years, range 10 to 18; 7 male, 10 female) with recurrent syncope and a positive head-upright tilt table test, and in whom standard therapies (fludrocortisone, transdermal scopolamine, beta-adrenergic blocking agents, disopyramide) were ineffective, poorly tolerated or contraindicated, were referred for study. Sertraline was administered orally at 50 mg daily for 4 to 6 weeks.

Results. Three patients (18%, 95% confidence interval [CI] 1 to 44) were intolerant of the drug, and it was discontinued. Nine patients became asymptomatic and tilt negative (53%, 95% CI 26 to 76), and five remained tilt positive (36%, 95% CI 15 to 65). Over a mean follow-up period of 12 ± 5 months, the tilt-negative patients remained symptom free while taking sertraline.

Conclusions. The serotonin reuptake inhibitor sertraline hydrochloride can be effective in preventing recurrent neurocardiogenic syncope in selected patients unresponsive to or intolerant of other therapeutic modalities.

A head-upright tilt table test was then reformed, and the clinical effect was noted.

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Recurrent unexplained syncope is a common and often frustrating clinical problem. Syncope annually accounts for up to 3% of all adult emergency room visits and 6% of all hospital admissions (1). Although the exact incidence of syncope in children and adolescents is unknown, it is thought to be similar (2). Since the introduction of clinical upright tilt table testing in 1986, it has become increasingly apparent that in many young patients, transient episodes of vasovagal mediately hypotension and bradycardia (neurocardiogenic syncope) are a frequent cause of their recurrent fainting spells (3). Recurrent episodes of sudden syncope can produce a high amount of anxiety among patients and their parents and teachers and may occasionally result in severe bodily injury (4). A recent study reported that the degree of functional impairment caused by recurrent syncope is comparable to that of chronic disabling disorders such as rheumatoid arthritis (5). Head-upright tilt table testing has greatly aided in identifying young patients susceptible to neurocardiogenic syncope and has been shown to be useful in assessing the adequacy of prophylactic therapy for the disorder (6–15). However, some patients who have recurrent neurocardiogenic syncope do not respond adequately to (or are intolerant of) the current available pharmacologic agents used to treat this problem, such as beta-adrenergic blocking agents, transdermal scopolamine, fludrocortisone and disopyramide. Recently, the serotonin (5-hydroxytryptamine) reuptake inhibitor fluoxetine hydrochloride has been reported to be effective in up to 53% of adult patients with recurrent neurocardiogenic syncope who were intolerant of or unresponsive to other forms of therapy (10). Thus, to determine whether serotonin reuptake inhibitors would have similar effects in children and adolescents with recurrent refractory neurocardiogenic syncope and positive head-upright tilt table tests, the following study was undertaken.

Methods
Seventeen patients with recurrent unexplained syncope were included in this study. Syncope was defined as an abrupt transient loss of consciousness with an inability to maintain postural tone. Each of the patients had had at least three syncopal episodes in the preceding 6-month period, the etiology of which remained unclear despite a complete history and physical examination, 12-lead electrocardiogram (ECG), echocardiography and electroencephalography. Twelve of the patients had undergone computed axial tomography of the brain, and four underwent magnetic reso-
nance imaging (MRI) of the brain. Seven patients underwent exercise tolerance testing. One patient underwent cardiac catheterization and coronary angiography.

Each of the 17 patients underwent head-upright tilt table testing after an overnight fast. The head-upright tilt table test protocol used has been described elsewhere (2,6). The study protocol was approved by the Institutional Review Board, and informed consent was obtained from the patient or parents, or both. Patients were then connected to a standard ECG monitor for continuous evaluation of heart rate and rhythm. A standard sphygmomanometer was used to measure blood pressure. Respiratory rate was determined every 3 min by direct observation. After baseline determinations of blood pressure and heart rate, each patient was positioned at an angle of 80° from horizontal for up to 30 min on a weight-bearing tilt table. Blood pressure was measured every 3 min, and ECG recordings were done continuously. If syncope occurred during the tilt, the patient was rapidly lowered to the supine position, and the study ended. If no syncope occurred during the tilt, the patient was lowered to the supine position for 5 to 10 min, and an intravenous isoproterenol infusion was started at 1 μg/min. Upright tilt table testing was then performed as previously described for a period of 20 min. If it was negative, a third tilt at 2 μg/min was performed. A positive response was described as the provocation of hypotension and bradycardia associated with a loss of consciousness that reproduced the patients' clinical episodes.

Standard therapies. Each of the 17 patients who were included in the study exhibited a positive response during head-upright tilt table testing. Each patient received standard pharmacotherapy, and repeat tilt table testing was performed to access response. The following agents were evaluated (unless contraindicated) in this order: fludrocortisone, 0.1 mg orally twice a day; atenolol, 50 to 100 mg orally once a day; transdermal scopolamine patch every 3 days; and disopyramide, 200 mg, controlled-release form, orally twice a day. Restudy was performed between 5 and 14 days after the initiation of a particular therapy. Failure was defined as the recurrence of syncope during tilt table testing or a clinical recurrence of syncope.

In each of the 17 patients, therapy with fludrocortisone, beta-blockers, transdermal scopolamine or disopyramide (either alone or in combination) was either contraindicated, poorly tolerated or ineffectual in preventing recurrent clinical syncope or upright tilt-induced syncope. In addition, each of the patients continued to experience episodes of syncope.

Sertraline administration. Each of the 17 patients (and their parents) with recurrent syncope and positive tilt table studies who failed to respond to conventional therapies agreed to participate in the study. Sertraline hydrochloride was started at 50 mg orally each day. Four to six weeks later, the response to head-upright tilt was reevaluated in the same laboratory at approximately the same time of day using the same protocol.

Data analysis. Results are expressed as mean values ± SD. Patients were classified as positive or negative for both the tilt study and their clinical course on the basis of whether their syncope symptoms occurred. The sample proportions for patients who were classified as negative on the basis of the absence of syncope were analyzed using the binomial distribution. Confidence intervals for the binomial proportions were calculated using the exact binomial distribution, and the reported 95% confidence intervals were based on the 1.96 SE of the proportion. Analysis of variance was used to determine whether there was a statistical significance between the groups on the basis of age, number of syncopal episodes and tilt time in phase. Contingency table analysis was used to establish whether there was an association between the syncope groups on the basis of gender breakdown.

Results

None of the 17 patients studied (10 young women, 7 young men; mean [±SD] age 15 ± 6.8 years, range 10 to 18) had any evidence of organic heart disease. Electrocardiography and echocardiography were normal in all patients. No patient had abnormal computed axial tomography or MRI of the brain or a history of depression. Four patients had a history of hyperactive airways disease, and six a history of recurrent severe headaches.

The mean number of syncopal episodes in the group was 6.8 ± 3.6 during the 6 months before the study. Two patients had been involved in automobile accidents as a result of syncope, one in a motorcycle accident, and one in a bicycle accident. One patient had a severe nasal fracture during syncope (requiring reconstructive surgery); one had a fracture of the clavicle after falling down a set of stairs; and one had a zygomatic arch fracture after syncope while showering. One patient had severe facial lacerations after falling onto gravel. In each of these patients, the clinical episodes were described as a sudden loss of consciousness occurring with little or no prodrome. Five of these adolescents had been banned from returning to public school, and all had been excluded from physical education or extracurricular activity. Two patients lost their part-time employment because of syncope.

Response to tilt table testing (Table 1). In response to head-upright tilt table testing alone (baseline study), 11 of the patients experienced syncope (64%) similar to what they had experienced clinically. The mean tilt time for the baseline positive patients was 16 ± 8 min. After upright tilt table testing with a graded isoproterenol infusion, six additional patients experienced syncope. The mean time to syncope was 12 ± 5 min. Two patients (Patients 2 and 10) had asystolic periods during tilt table testing.

Response to sertraline therapy. Three patients developed side effects and eventually asked to be discontinued from the drug. Two had complaints of nausea and diarrhea, and one complained of headaches and nausea. The remaining 14
patients tolerated the drug well, although three patients complained of some mild difficulty sleeping (but not enough to discontinue use of the agent).

Twelve patients reported having no clinical syncopal episodes up to 4 weeks after starting the drug (the minimal time to see an effect with sertraline) and the follow-up tilt study. Two patients reported syncopal episodes during the same period.

In response to repeat tilt table testing, nine patients (53%, 95% confidence interval (CI) 26 to 76) were rendered negative; the remaining five patients (36%, 95% CI 15 to 65) continued to have induced hypotension and bradycardia.

The patients who were rendered tilt negative during sertraline therapy continued to receive it. Over a mean follow-up period of 12 ± 5 months, these patients have remained symptom free (one patient had a syncopal spell after stopping sertraline but has had none since its resumption, and one patient discontinued taking sertraline after moving to another city and has since had recurrent syncopal spells).

Of the patients who were intolerant of, or had failed, sertraline therapy, three have continued to experience recurrent syncope, one has had no further episodes with a combination of support hose, fluorohydrocortisone and theophylline, and one has been lost to follow up. Three patients who were tilt positive on sertraline asked to continue the drug; only one has had recurrent syncope.

**Discussion**

Recurrent episodes of neurocardiogenic syncope can be a severely disabling condition for a young person (2). The unpredictable nature of these episodes not only creates an extreme psychologic burden for the patient and their families, but may also limit the young person's educational and employment opportunities (5).

Although the majority of patients who require pharmacotherapy will respond to the standard treatment modalities, such as fludrocortisone (6), beta blockers (16), theophylline (17), disopyramide (18), transdermal scopolamine (19) and pseudoephedrine (20), there are patients for whom these drugs are ineffective, poorly tolerated or contraindicated. On the basis of our initial observations in adult patients that fluoxetine hydrochloride, a serotonin reuptake inhibitor, prevented upright tilt-induced syncope in ~50% of otherwise refractory patients, we decided to explore the potential usefulness of serotonin reuptake inhibitors in a similar group of pediatric patients with recurrent refractory neurocardiogenic syncope (10). The data presented here demonstrate that sertraline hydrochloride was clinically significant in preventing upright tilt-induced neurocardiogenic hypotension and bradycardia in nine (53%) of 17 young patients with recurrent syncope (or nine [64%] of 14, 95% CI 35 to 86, p = 0.04) who tolerated the drug.

Recurrent unexplained syncope in the young patient is frequently believed to be neurocardiogenic (or vasovagal) in nature. Head-upright tilt table testing has been introduced as a promising method of identifying patients predisposed to neurocardiogenic hypotension and bradycardia (2). The results of head-upright tilt table testing have been demonstrated to be reproducible and have been used as a guide to the efficacy of pharmacotherapies used to prevent recurrent syncope (11-13). Although the exact mechanism by which syncope occurs is still poorly understood, it is presently...
thought that a sudden increase in the degree of peripheral vasodilation results in a sudden decrease in venous return to the heart, leading to a rapid increase in the force of ventricular contraction (14). This increase in contractile force is postulated to cause the activation of a large number of mechanoreceptors located in the base of the right and left ventricles. This dramatic increase in afferent neural traffic to the brain stem seems to mimic the conditions that occur during hypertension and produces an apparent "paradoxical" reflex bradycardia and peripheral vasodilation (15).

Therapy. Therapy for the young patient with recurrent neurocardiogenic syncope must be individualized for each patient because the severity of the condition varies widely. In many young patients, syncope only occurs under exceptional circumstances, and the patient need only be advised to avoid predisposing conditions. Some patients will experience a definite prodrome before syncope and can be advised to lie down when they think an episode is imminent (15). However, there are some patients with recurrent and unpredictable syncope that occurs with little or no warning. Pharmacotherapy is required in this group.

Usually, most young patients who require pharmacotherapy will respond to one (or a combination) of the aforementioned agents. Yet, there are patients in whom these drugs are ineffective, poorly tolerated or contraindicated. Similar problems in older adult patients led us to investigate the use of the serotonin reuptake inhibitor fluoxetine hydrochloride after anecdotal observations that patients receiving the drug as therapy for depression showed a marked improvement in their neurocardiogenic syncope (10). In 16 patients with recurrent refractory neurocardiogenic syncope who were treated with fluoxetine hydrochloride, 20 mg orally, each day for 5 to 6 weeks, three developed side effects requiring discontinuation (headaches, nausea and sexual dysfunction). Overall, seven (44%) of 16 patients became tilt negative and asymptomatic (or seven 53% of 13 who tolerated the drug). These observations led us to test the effectiveness of a similar serotonin reuptake inhibitor, sertraline hydrochloride, in the therapy of young patients with severe refractory neurocardiogenic syncope. We found the overall response rate in this group was similar: nine (53%) of 17 patients were rendered tilt negative and asymptomatic, and three (17%) of 17 proved intolerant of the agent, mainly because of headaches and nausea.

Serotonin and syncope. The exact part played by serotonin pathogenesis of neurocardiogenic syncope is unclear. However, serotonin has been shown to be an important component of the responses seen as a result of acute blood loss, a mechanism essentially similar to that of neurocardiogenic syncope (14,21). Using an anesthetized cat model, Elam et al. (22) found that depletion of serotonin stores blunts the sudden decrease seen in arterial pressure and heart rate during acute hemorrhage. Further studies have shown that the administration of the serotonin receptor blocker methysergide during acute hemorrhagic hypotension has a marked pressor effect (22). Similar studies by Hasher et al. (23) have demonstrated that methysergide increased blood pressure when given to conscious rabbits made hypotensive by acute hemorrhage. Morgan et al. (24,25) have reported similar findings and suggested that sympathoinhibitory serotoninergic mechanisms in the central nervous system may be stimulated by acute hemorrhage, thereby producing vasodilation and bradycardia. Abboud (14) recently reported that central intracerebrovascular serotonin induces hypotension, inhibition of renal sympathetic nerve activity and excitation of renal sympathetic nerve activity. He further stated that these studies raise the possibilities that serotonin may be acting at a central level to inhibit sympathetic activity and that serotonin antagonists may be effective in the treatment of neurocardiogenic syncpe.

Sertraline hydrochloride (Zoloft, Pfizer) is a relatively new selective serotonin reuptake inhibitor (26). In contrast to the tricyclic antidepressant compounds, sertraline is characterized by highly selective serotonin reuptake inhibition with little or no affinity for adrenergic, cholinergic or histamine receptors (27). It is also considered a much more potent serotonin reuptake blocker than fluoxetine hydrochloride (Prozac) (28). Peak plasma concentrations of sertraline are achieved between 6 and 8 h after oral administration, and the drug is 98% bound to plasma proteins (29). The primary metabolite of sertraline is desmethylsertraline, which is eight times less potent a serotonin reuptake blocker than the parent compound (27). Sertraline has an elimination half-life of ~26 h; that of desmethylsertraline is ~66 h (28). Steady-state concentrations are believed to require at least 4 weeks of therapy (26).

We chose to use sertraline rather than fluoxetine in this group because of the drug’s greater degree of serotonin reuptake inhibition and reported lower side-effect profile (26,27). We also thought that the relatively small sertraline tablets would be easier for the young patient to swallow (rather than the much larger fluoxetine capsules).

In our study group, however, the percent of patients requiring discontinuation of the drug as a result of side effects was the same as we observed with fluoxetine, ~18% (10). The most common side effects seen during sertraline therapy include nausea, diarrhea and insomnia (20).

Overall, we found sertraline to be a safe and effective therapy for preventing head-upright tilt induced syncope in young patients unresponsive to, or intolerant of, other therapies. The exact mechanisms by which both sertraline and fluoxetine exert their effects remain uncertain. We postulate that through the enhancement of serotoninergic transmission, these agents may induce a down-regulation of postsynaptic serotonin receptors, thereby blunting the potential response to rapid shifts in cerebral serotonin levels (10). Beta-blockers have recently been shown to have central serotonin-blocking activities, an action that may contribute to their therapeutic effect in neurocardiogenic syncope (30,31).

Study limitations. There were several important limitations to our study. The study group was relatively small,
and it was not a randomized, controlled trial. Rather, each patient was used as his or her own control. Side effects precluded continuation of the drug in three patients. Because the effects of sertraline on human fetal development are unknown, female patients should be advised not to become pregnant while taking sertraline. In addition, neurocardiogenic syncope may exhibit spontaneous variations in severity (15). Therefore, we cannot be sure that the beneficial effects noted can be wholly attributed to the actions of the drug. Furthermore, the patients presented here tended to have an unusually severe form of neurocardiogenic syncope and thus may not be representative of the majority of patients with this disorder.

Conclusions. We conclude that sertraline hydrochloride may be an effective therapy in young patients with recurrent episodes of neurocardiogenic and upright tilt-induced hypotension and bradycardia who are unresponsive to or poorly tolerant of other therapies. Additional randomized, controlled studies will be necessary to better define the potential role of serotonin reuptake inhibitors in the management of neurocardiogenic syncope and to understand the exact mechanisms by which these effects occur.

References