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EDITORIAL COMMENT

Finally, a Drug Proves to Be Effective Against Vasovagal Syncope!

But Not in All Patients*

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Many drugs have been tested for the treatment of vasovagal syncope; for the most part, the results have been disappointing. The list includes beta-blockers, disopyramide, scopolamine, theophylline, ephedrine, etilefrine, midodrine, clonidine, and serotonin reuptake inhibitors. Although results have been satisfactory in uncontrolled trials or short-term controlled trials, the few long-term placebo-controlled prospective trials conducted have been unable to show a benefit of the active drug over placebo.

For example, because failure to achieve proper vasoconstriction of the peripheral vessels commonly occurs in reflex syncope, alpha-agonist vasoconstrictors (etilefrine and midodrine) have been used. Etilefrine has been studied in a large randomized, placebo-controlled, double-blind clinical trial (1). During follow-up, patients treated twice daily with etilefrine 25 mg or placebo showed no difference in the frequency of syncope or the time to recurrence. Midodrine has proved effective in 4 small studies (2), but none of these satisfied the criteria of a pivotal clinical trial. Beta-blockers have been advocated in vasovagal syncope on the presumption that they lessen ventricular mechanoreceptor activation owing to their antisympathetic and negative inotropic effect in reflex syncope. However, beta-blockers failed to be effective in 2 randomized double-blind controlled trials (3,4), and the underlying rationale has been questioned.

The results of the POST 2 trial (Prevention of Syncope Trial 2), a randomized, double-blind, placebo-controlled study of fludrocortisone in the prevention of vasovagal syncope, are presented in this issue of the *Journal* (5). This is an important study because,

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for the first time, a drug has been demonstrated to reduce recurrences of vasovagal syncope in young patients (median age 30 years) affected by moderately frequent vasovagal syncopes. The primary endpoint showed only a marginal nonsignificant reduction in syncope in the fludrocortisone group compared with the placebo group (hazard ratio: 0.69; 95% confidence interval: 0.46 to 1.03; $p = 0.069$). However, the difference became more significant in an exploratory subgroup analysis restricted to outcomes after 2-week dose stabilization and to those patients who achieved 0.2-mg dose stabilization at 2 weeks. The evidence of benefit was reinforced by a strong underlying pathophysiological rationale. Indeed, vasovagal syncope is often preceded by orthostatic stress, pooling of venous blood in the lower limbs, ineffective venoconstrictive responses, and decreased venous return and pre-load, which in turn reduces cardiac output, causing hypotension and reduced cerebral perfusion (6–8). By increasing renal sodium reabsorption and expanding plasma volume, fludrocortisone counteracts this mechanism and blocks the physiological cascade leading to the vasovagal reflex. The mechanism of action is similar to that of saline infusion, which has also proved to be effective in short-term tilt-test studies (9,10).

WILL THE POST 2 TRIAL CHANGE CURRENT CLINICAL PRACTICE?

In the POST 2 trial, the clinical benefit of fludrocortisone therapy was modest and the risk of

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potential adverse effects elevated. Moreover, at 12 months, 44.0% of patients in the fludrocortisone arm continued to experience syncopal spells, a rate only slightly lower than the 60.5% rate observed in the patients in the placebo arm. This corresponds to a difference of 12 patients between the 2 groups (42 of 105 vs. 54 of 105) and to a number needed to treat of about 6. In the meantime, a similar number of patients discontinued fludrocortisone therapy because of side effects, thus equalizing the benefit/risk ratio. Drug titration was particularly challenging. As per protocol, treatment started with 0.1 mg of the study drug daily, with the intent to increase to 0.2 mg daily within 5 to 14 days. However, patients who were intolerant of the study medication had their dose reduced to 0.05 mg daily.

Fludrocortisone is expected to have other important adverse effects which, owing to the study design, could not be fully assessed. As per protocol, patients with significant comorbidities, a permanent pacemaker, glaucoma, diabetes mellitus, hepatic disease, or blood pressure ≥130/85 mm Hg were excluded. Although no upper age limit was defined in the protocol, the actual median age of enrolled patients was 30 years, suggesting that the investigators themselves were not confident about prescribing long-term fludrocortisone for older patients. The authors were well aware of the side effects of the drug and wisely recommended that it should not be used in patients with hypertension or heart failure.

WOULD THE BENEFIT BE GREATER IF FLUDROCORTISONE WERE PRESCRIBED FOR A SELECTED POPULATION?

Probably, yes. This is a typical study in which some patients benefit from the therapy, whereas others do not or must discontinue it because of side effects. Fludrocortisone is not for all patients with vasovagal syncope. Learning to identify responders will be crucial to acceptance of this therapy by the scientific community and will be the subject of future research. However, some indications are already suggested by the results of the POST 2 trial. Because the biological effect of fludrocortisone is to increase renal sodium reabsorption and expand plasma volume, thereby increasing arterial blood pressure, such therapy seems particularly appealing for patients in whom hypotension is a predisposing factor for vasovagal syncope. The average baseline supine blood pressure was rather low, around 113 mm Hg (interquartile range: 104 to 120 mm Hg), and was lower than that of similar patients affected by vasovagal syncope enrolled in the POST 1 trial (129 mm Hg) (4) and the VASIS (Vasovagal Syncope International Study) (130 mm Hg) (1). Compared with the patients of these latter studies, POST 2 patients had more syncopal episodes and, on average, were 10 years younger. Moreover, in a subgroup analysis, the authors found that the patients who benefitted most were those who had low baseline systolic blood pressure <110 mm Hg (hazard ratio: 0.48). These findings suggest that the patients in the POST 2 trial were partly different from those of the general population of patients with vasovagal syncope. Indeed, they seem to have clinical features overlapping with hypotensive syndrome of the young adult.

Despite several limitations and precautions, which are clearly acknowledged by the authors themselves, the POST 2 trial provided convincing data supporting the benefit of fludrocortisone for the prevention of syncopal recurrences, especially in young patients with low-normal values of arterial blood pressure and without comorbidities. The study cannot be considered conclusive; indications, benefit, and risk need to be assessed in larger studies with longer follow-up. However, thanks to the POST 2 trial results, fludrocortisone fills an important gap in the medicine cabinet, which contains few therapies for vasovagal syncope that have passed the test of evidence limited to controlled clinical trials.

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