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EDITORIAL COMMENT

Can an Intranasal Calcium-Channel Blocker Convert Paroxysmal Supraventricular Tachycardia and Keep the Doctor Away?*

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Paroxysmal supraventricular tachycardia (PSVT) is generally a narrow-complex regular tachycardia that excludes atrial flutter and atrial fibrillation (1,2). Atrioventricular (AV) nodal and AV re-entrant tachycardia are secondary to discrete electric pathways, which are present from birth, and structural heart disease is usually absent or not a causative factor. The 2 most common types of this arrhythmia (AV nodal re-entry and AV re-entry) are AV node dependent and can have persistent episodes terminated by vagal maneuvers or intravenous, nondihydropyridine calcium-channel blockers, or adenosine (1,2). About 10% of regular supraventricular tachycardias (SVTs) are not AV node dependent and include atrial-origin tachycardia. Abrupt initiation and termination are typical of PSVT.

The frequency of PSVT depends on the frequency of triggers, the characteristics of the pathways involved, and the extent of their excitable gap. Typical symptoms include palpitations, lightheadedness, and chest pain. Hemodynamic compromise can occur but is uncommon.

The incidence of PSVT is about 36 per 100,000 persons (3). About 570,000 people in the United States have PSVT, with about 89,000 new patients diagnosed (3) and 50,000 annual emergency department visits per year (4). A 10-year review of treatment patterns in the emergency department reported that about 50% of these patients were treated with AV node-blocking agents, 24% of patients were hospitalized, and 44% were discharged with no planned follow-up (4). Physicians can have a difficult time making a correct diagnosis of PSVT, and this can expose patients to inappropriate therapy and unnecessary testing. In 1 emergency department study, 38% of patients were given adenosine inappropriately for atrial fibrillation or flutter, sinus tachycardia, and in 2 cases for ventricular tachycardia (5). Besides a classic history, 12-lead electrocardiography is helpful in the evaluation of SVT. The morphology and relationship between P waves and the QRS complex (PR or RP) are helpful in making a more specific diagnosis (2).

Acute management of SVT focuses on termination or conversion to sinus rhythm and/or control of the ventricular rate (1,2). Direct-current cardioversion is reserved for patients with hemodynamic compromise or in whom medical therapy is ineffective or not feasible (Class I, Level of Evidence: B-NR) (1). Vagal maneuvers can be helpful in terminating or in revealing clues to the etiology of the arrhythmia (Class I, Level of Evidence: B-R) (1). L-type calcium-channel blockers decrease conduction velocity and prolong the antegrade AV node-refractory periods, helping terminate an AV node-dependent SVT. These drugs can also terminate atrial tachycardia, which is caused by triggered activity. Intravenous verapamil and diltiazem (Class I, Level of Evidence: B-R) (1) are efficacious for acute management of narrow-complex

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hemodynamically stable SVT but can cause hypotension. In addition, AV node effects may last long enough to minimize SVT recurrences after conversion or at a minimum slow the ventricular rate if SVT is not terminated. Adenosine is an A1 receptor agonist in cardiac muscle cells that prevents the influx of calcium into the cell and thus depresses conduction of the sinoatrial node and AV node. In a double-blind, randomized, placebo-controlled trial, adenosine was as efficacious and safe as verapamil (6), but the time to termination with adenosine was faster, occurring in 30 s. Adenosine is an effective treatment (86% to 96%) for the acute termination for narrow-complex SVT (Class I, Level of Evidence: B-R) (1); however, because of its short half-life, SVT can recur. Adenosine can also terminate atrial tachycardia because of triggered activity. Thus, similar to calcium-channel-blocking agents, termination of tachycardia by the drug makes it likely the arrhythmia was AV node dependent but not diagnostic. Beta-blocking agents have a limited role in the acute treatment of PSVT, mainly in post-operative patients with high adrenergic states, but are still recommended in the guidelines (Class IIa, Level of Evidence: C-LD) (1).

Catheter ablation for the treatment of recurrent PSVT, with cure rate of >90% to 95%, is a frontline alternative to pharmacological therapy in very symptomatic patients, especially in young women who are anticipating pregnancy or in patients with high-risk professions seeking a definitive cure (1,2). However, catheter ablation has no acute role in treating PSVT except for in the rare occurrence of incessant SVT.

Some patients have rare occurrences of well-tolerated SVT that last long enough for patients to present for emergency treatment. Thus, a major gap in our therapeutic armamentarium against PSVT has been the absence of a short-acting, antiarrhythmic drug that does not need to be given parenterally. Attempts to use pill in the pocket with oral diltiazem or propranolol terminated SVT, with a mean time of 39 min, better than placebo (7). Alboni et al. (8) evaluated the conversion rate and safety profile of a single, crushed, oral dose of flecainide, diltiazem and propranolol, and placebo in 33 patients with inducible SVT during electrophysiology studies. The conversion rates, within 2 h, were 52% for placebo, 61% with flecainide, and 94% with a combination of diltiazem and propranolol. However, time to conversion was a mean of 32 min with diltiazem and propranolol and 74 min with flecainide. Patients were discharged on the most effective medication for conversion and instructed to take medication 5 min after the onset of symptoms and go to the emergency department if the tachycardia persisted for >2 h. Using this approach, 1-year emergency department consultation decreased from 100% at baseline to 9%. Adverse events included rare hypotension, bradycardia, and 1 episode of syncope.

In this issue of the *Journal*, Stambler et al. (9) report on the efficacy of intranasal etripamil, a rapid-onset, short-acting ($T_{1/2}$ <5 min), L-type calcium-channel-blocking agent and its efficacy in terminating induced PSVT in the electrophysiology laboratory.

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Nasal delivery of medications can minimize poor bioavailability, slow absorption, drug degradation, and adverse events in the gastrointestinal tract and avoids the first-pass metabolism in the liver (10). Some limitations of this phase 2 study include that all patients were treated in a controlled environment with induced tachycardia of >5 min duration and a known re-entrant mechanism. Patients with concomitant medications and structural heart disease were excluded. Almost one-half of the patients failed to be enrolled because of the inability to induce or sustain SVT, and 87% of patients had AV nodal re-entrant tachycardia. Results may differ in patients who take etripamil after longer periods of SVT, and etripamil probably should be avoided in patients with recurrent SVT spells that historically terminate within a few minutes. Even in this controlled trial, there was a high (35%) placebo conversion rate. The 70-mg dose seemed to have the best balance of efficacy (87% conversion rate within 15 min) and safety. The median time to conversion was <3 min. Higher doses were associated with some hypotension, and there was 1 case of AV block that persisted for >30 min. Patients were excluded if their baseline systolic blood pressure was <100 mm Hg. This raises the issue of how patients in the outpatient setting will know their blood pressures. The short duration of action of intranasal etripamil may minimize the duration or severity of any hypotensive spells. A history of syncope may be a contraindication to the use of this approach.

Further studies in the real world, including the emergency department, need to be performed to demonstrate the safety and efficacy of intranasal etripamil. Most patients receiving this therapy will not have electrophysiology laboratory diagnoses of their arrhythmias. If one is going to use intranasal etripamil for acute termination of SVT, either as an outpatient or in the emergency department, one will still have to exclude appropriate or inappropriate sinus tachycardia or other atrial-origin tachycardia that will not respond to this therapy. Before prescribing this therapy, patients may need to have an initial trial of this therapy in a controlled telemetry environment. If the therapy is ineffective or SVT recurs,

the patient will need to be instructed to seek medical attention.

Keeping patients away from the emergency department or unnecessary chronic antiarrhythmic therapy or ablation procedures for infrequent attacks will be the biggest benefit of this therapy. Defining the right patient population and the most efficacious and safe dose will be an important part of clinical trials. Given the transient circulation of the drug, long-term adverse effects will be unlikely and of little concern to the regulatory bodies. The drug will need to have a fairly long shelf-life, because the therapy will be used uncommonly. Given the high cost of ineffective chronic antiarrhythmic therapy or an effective ablation, the cost of this therapy will be much less than a visit to the emergency department or alternative therapeutic approaches.

Current guidelines suggest vagal maneuvers prior to any intravenous therapy (1). This will be the same if intranasal etripamil becomes available commercially. If phase 3 controlled studies can verify the safety and efficacy of this therapy, patients who have rare persistent recurrences of PSVT may be an ideal candidate for this therapy instead of taking daily antiarrhythmic therapy or an having an ablation procedure. The success of this therapy may increase the development of other intranasal cardiac medications for other arrhythmias or cardiac conditions. Intranasal etripamil would offer patients the ability to rapidly terminate SVT episodes without the need to visit a health care facility. Although this would be a niche therapy for select patients, such a treatment is long overdue.

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