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RESEARCH LETTER

Self-Administered Etripamil Nasal Spray Relieved Symptoms, Decreased Heart Rate, and Reduced Medical Interventions During Atrioventricular Nodal–Dependent Paroxysmal Supraventricular Tachycardia

Bruce S. Stambler, MD; Benoit Coutu, MD; James E. Ip, MD; Blandine Mondésert, MD; A. Shekhar Pandey, MD; Philip T. Sager, MD; Doug Wight, PhD; Francis Plat, MD; Silvia Shardonofsky, MD; David B. Bharucha, MD; A. John Camm, MD

Etripamil nasal spray, a nondihydropyridine, fast-acting, calcium channel blocker, formulated to be self-administered, is in development for the acute treatment of paroxysmal supraventricular tachycardia (PSVT). NODE-301 Part 1, a randomized, double-blind, placebo-controlled study, evaluated the safety and efficacy of a 70 mg dose of etripamil among patients who self-administered the treatment outside the healthcare setting during symptomatic atrioventricular nodal–dependent PSVT.[1] Although the primary end point of conversion of PSVT to sinus rhythm within 5 hours was not demonstrated, analyses at shorter times including 30 minutes, consistent with the pharmacokinetics of the drug, indicated the effectiveness of etripamil to convert PSVT.[1] Etripamil was well tolerated with no serious adverse events within 24 hours of administering the study drug.[1] Here, we report key secondary and exploratory outcomes from NODE-301 Part 1 including relief of PSVT symptoms, need for additional medical interventions and emergency care for PSVT, and the effects on tachycardia heart rate before conversion.

Inclusion criteria, baseline characteristics, and methods for NODE-301 Part 1 study have been published.[1] Patients who were diagnosed with other arrhythmia substrates, including Wolff-Parkinson-White syndrome and ventricular tachycardia, were excluded from this study. Secondary end points assessed defined symptoms associated with PSVT. Patient-reported treatment satisfaction was measured using the Treatment Satisfaction Questionnaire for Medication-9,[2] a validated questionnaire of 9 questions with responses on a scale score of 1 (extremely dissatisfied) to 7 (extremely satisfied), converted to a score of 0 to 100 points for analysis of 3 domains: Effectiveness, Convenience, and Global Satisfaction. Exploratory end points included the proportion of patients requiring additional medical intervention, including emergency department care within the first 5 hours. An exploratory analysis assessed the effects of the study drug on tachycardia rate within the 60 minutes after drug administration or before conversion to sinus rhythm if that occurred <60 minutes. Tachycardia rates were captured in 1-minute increments from baseline (average of 4 values before drug administration) by an ambulatory monitor and adjudicated by an independent blinded committee. Data from 4 PSVT episodes that terminated within 1

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Correspondence to: A. John Camm, MD, St. George's University of London, Cardiology Clinical Academic Group, Molecular and Clinical Sciences Institute, Cranmer Terr, London, SW19 0RE, United Kingdom. Email jcamm@sgul.ac.uk

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Nonstandard Abbreviations and Acronyms	
PSVT	paroxysmal supraventricular tachycardia

minute after administering the study drug (etripamil, n=3; placebo, n=1) and data from patients who had inadequate ECG data (etripamil, n=2) were excluded from this analysis. ANOVA was used for the Treatment Satisfaction Questionnaire for Medication analyses, including relief of symptoms as measured by the Treatment Satisfaction Questionnaire for Medication question 2 (Figure [B]). Furthermore, Fisher exact test was used for the medical interventions and mixed models with repeat measures for change in heart rate before conversion (Figure [C]). For mixed models with repeat measures, treatment, time, and time treatment interaction were the fixed variables, and heart rate was the dependent variable. The study was approved by Institutional Review Boards at participating sites; all participants provided written informed consent before participation. The data that support the findings of this study are available from the corresponding author on reasonable request.

Of the patients (N=156) who had confirmed PSVT, 107 were in the etripamil and 49 in the placebo group (reflecting 2:1 randomization). Most patients (>75%) reported rapid pulse and palpitations during PSVT episodes, before treatment. Other symptoms, reported by ≥20% of patients, included dizziness, shortness of breath, anxiety, and chest pain. Proportions of patients reporting individual symptoms pretreatment were similar between the study drug groups (Figure [A]). Patients receiving etripamil during a PSVT episode had significantly greater symptom relief versus patients receiving placebo (Figure [B]). The etripamil-treated group reported significantly higher Treatment Satisfaction Questionnaire for Medication-9 global treatment satisfaction and effectiveness scores than the placebo group (P<0.001, both measures). Patient-reported convenience scores were similar between etripamil and placebo groups (P=0.6), which reflects an equivalent intranasal delivery method of the study drug and placebo.

The baseline mean±SE heart rate during PSVT was 179±2.8 and 174±4.0 bpm for etripamil and placebo, respectively (P not significant). After study drug administration, the etripamil versus the placebo group had a significantly reduced mean heart rate from baseline during sustained PSVT episodes at 3 (P<0.03), 10 (P<0.0001), 30 (P<0.0002), and 40 minutes (P<0.004; Figure [C]). Maximal heart rate reduction from baseline occurred at 10 minutes in the etripamil group (−16±2.1 bpm; P<0.0001). Among patients treated with etripamil, maximal heart rate reduction from baseline during PSVT was positively correlated with symptom relief (R^2=0.090; P=0.0027) and treatment effectiveness satisfaction (R^2=0.086; P=0.0034).

In the etripamil group, the percentage of patients seeking additional medical intervention related to PSVT, including emergency department intervention and oral treatments, was numerically lower in the etripamil group versus the placebo group (27% versus 14%, respectively; P=0.12).

Etripamil nasal spray treatment improved symptoms and reduced tachycardia rate during PSVT, compared with placebo. Improved patient-reported symptomatic measures included treatment effectiveness and global satisfaction. The current data indicate an etripamil treatment-effect in converting PSVT to sinus rhythm with rapidity, consistent with the pharmacokinetics of the drug and support continued investigation of etripamil nasal spray for self-administration during PSVT in a medically unsupervised self-treatment.

ARTICLE INFORMATION

Affiliations

Piedmont Heart Institute, Atlanta, GA (B.S.S.). Centre Hospitalier de l'Université de Montréal, QC, Canada (B.C.). Weill Cornell Medicine, New York Presbyterian Hospital, NY (J.E.I.). Montreal Heart Institute, Université de Montréal, QC, Canada (B.M.). Cambridge Cardiac Care Centre, ON, Canada (A.S.P.). Stanford University School of Medicine, Palo Alto, CA (P.T.S.). Milestone Pharmaceuticals, Montreal, QC, Canada (D.W., F.P., S.S., D.B.B.). St. George's University of London, United Kingdom (A.J.C.).

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Disclosures

Dr Stambler is on the steering committee for Milestone Pharmaceuticals. Dr Ip received compensation as study investigator and steering committee member for Milestone Pharmaceuticals; received honoraria/speaking/consulting fees for Abbott Medical, Boston Scientific, and Medtronic, Inc; has membership on the advisory committee and steering committee for Abbott Medical and Medtronic, Inc; has membership on data safety monitoring committee for Boston Scientific. Dr Mondésert is a consultant for Milestone Pharmaceuticals. Dr Sager has equity in Milestone Pharmaceuticals. Dr Wight was an employee of Milestone Pharmaceuticals. Dr Plat is an employee of Milestone Pharmaceuticals. Dr Shardonofsky is an employee of Milestone Pharmaceuticals. Dr Bharucha is an employee of Milestone Pharmaceuticals. Dr Camm is a consultant and serves on the steering committee for Milestone Pharmaceuticals; has received grants and personal fees from Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Daiichi Sankyo, and Pfizer; has received personal fees from Biotronik, Boston Scientific, and Menarini; and has received support from Abbott, Anthos, GlaxoSmithKline, Johnson & Johnson, and Sanofi. The other authors report no conflicts.

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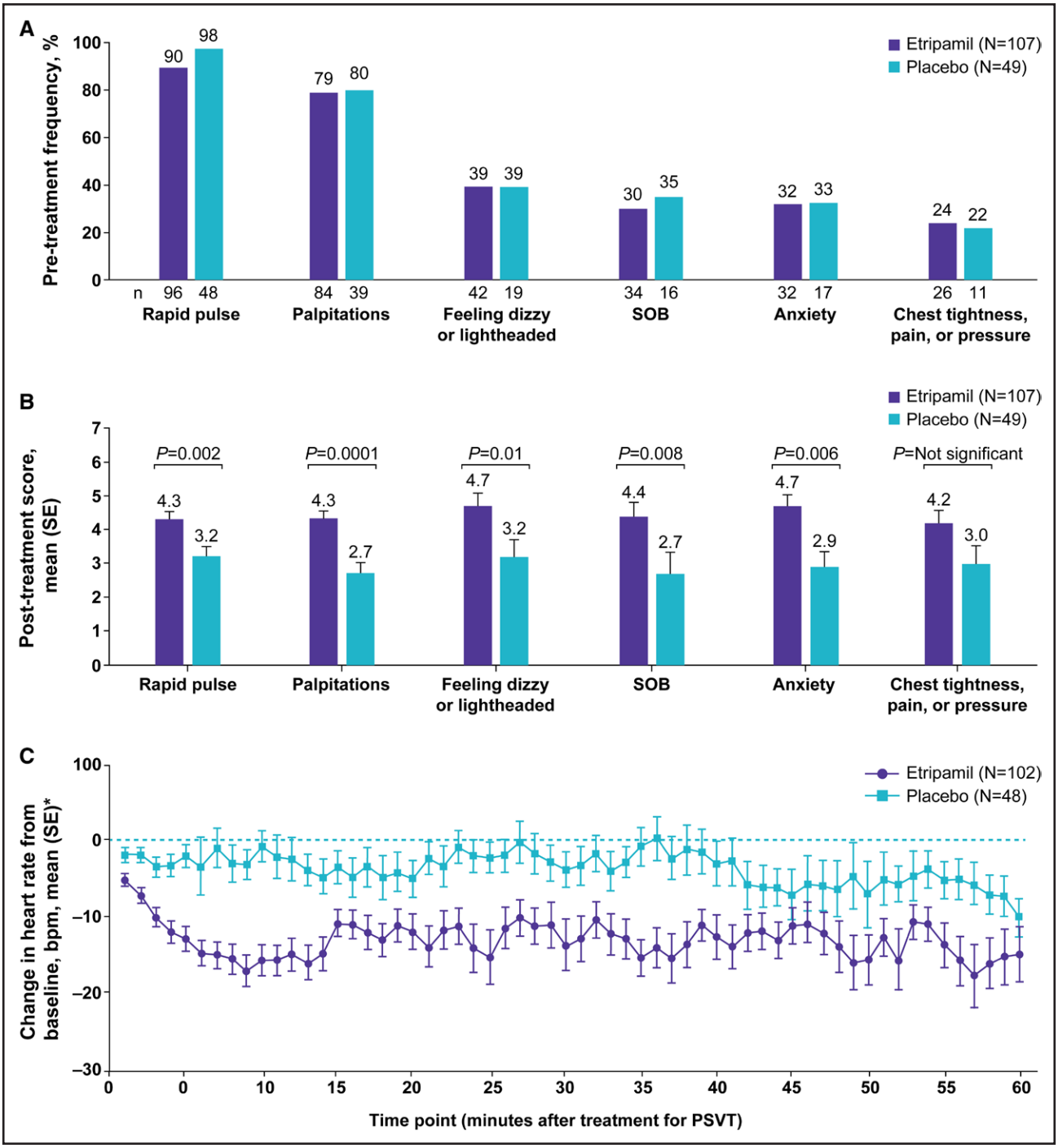

Figure. Secondary outcomes reported in the NODE-301 study: etripamil 70 mg or placebo was administered to treat paroxysmal supraventricular tachycardia (PSVT; N=156).

Participants reported individual symptoms before the treatment of adjudicated PSVT in the NODE-301 Part 1 study (**A**); treatment satisfaction scores for participants who received etripamil 70 mg or placebo to treat adjudicated PSVT (**B**); and change in heart rate assessed by mixed models with repeat measures (MMRM) after study drug administration during adjudicated PSVT (**C**). SOB indicates shortness of breath.