

Effect of Etripamil Nasal Spray on Ventricular Rate in Patients Experiencing Symptomatic Atrial Fibrillation

NODE-303 Atrial Fibrillation Heart Rate Analysis

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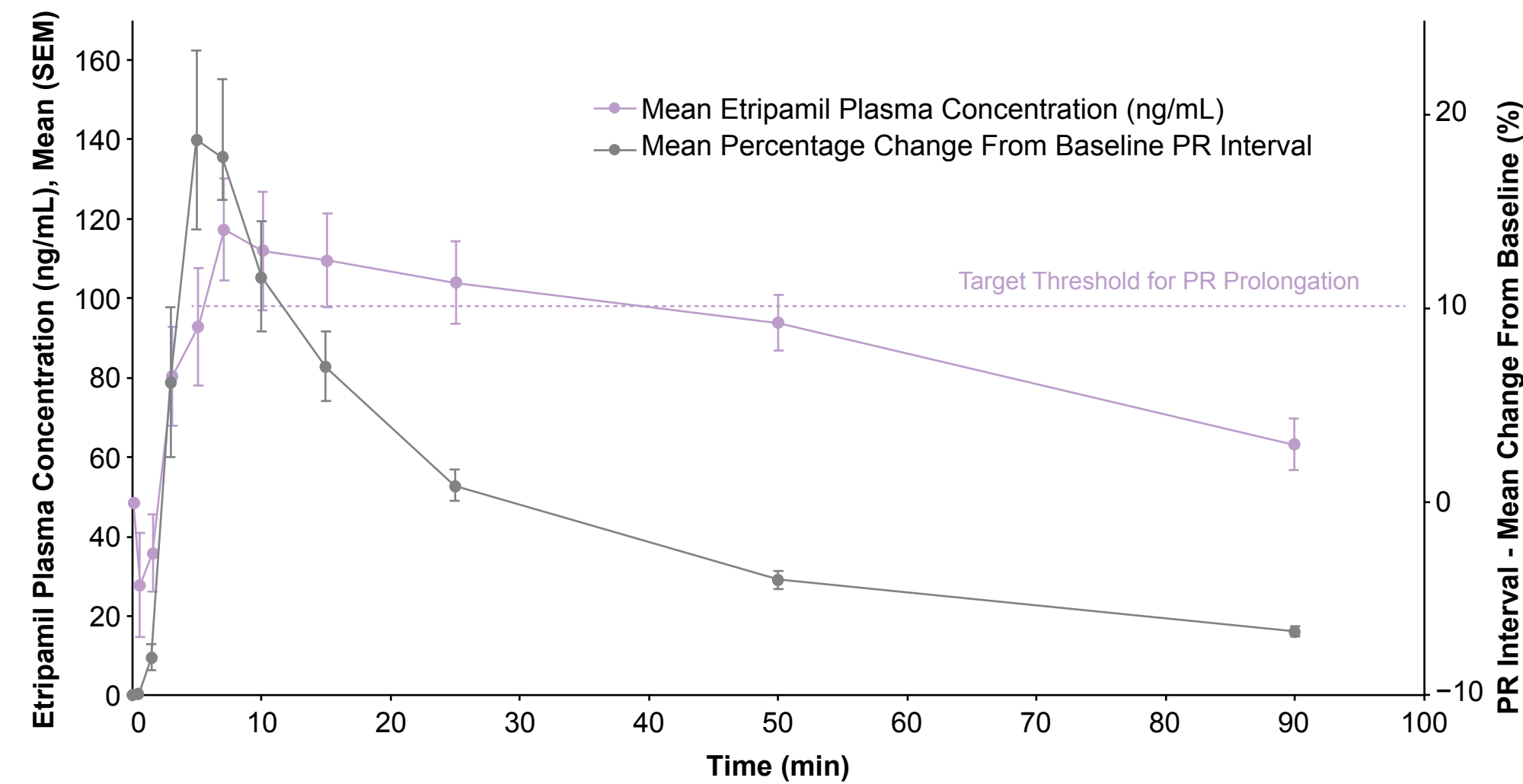
Atrial Fibrillation With Rapid Ventricular Response (AF/RVR)

- AF is the most common sustained arrhythmia
 - An estimated 2.7 to 6.1 million people in the United States have AF, with projections to reach nearly 12.1 million in 2030¹
- Often, symptoms are due to a RVR, especially in younger patients
- Patients with rapid rates often seek urgent medical care; immediate treatment is usually rate control with intravenous AV nodal blockers
 - Rate control in patients with AF is an important strategy to reduce symptoms, to improve quality of life, and is often needed acutely even if a rhythm control approach is planned
- There are no available rapidly acting agents to slow ventricular rates suitable for outpatient self-administration

Etripamil Nasal Spray

- Etripamil is a novel, formulated, intranasal calcium channel blocker with rapid onset of action ($T_{max} \leq 7$ min) under investigation for reentrant supraventricular tachycardia (SVT)
 - Formulated for intranasal self-administration
 - Rapid onset of action ($T_{max} \leq 7$ min)
 - Inactivated by blood esterases
 - In development to support regulatory filings for the acute treatment of paroxysmal supraventricular tachycardia (PSVT)
 - In Phase 2 development for the acute treatment of AF with RVR

Comparison of PK and PD Profile of Etripamil 70 mg (N = 24)



Anticipated therapeutic effect within 45 minutes, peak within 10 minutes
PR interval prolongation is a marker of AV conduction time

AV = atrioventricular; PK = pharmacokinetic; PD = pharmacodynamic; PR = P wave, R wave; T_{max} = time to peak drug concentration. Error bars indicate standard error of the mean.

NODE-303: Open-Label, Phase 3 Trial of Etripamil for SVT

Trial Design

- Event-driven, multi-center, open-label, multi-exposure study to evaluate the safety of etripamil in patients with PSVT
- Patients perceived PSVT episodes as outpatients and self-administered etripamil nasal spray (70 mg)
- Continuous ECG data (patient-applied) were acquired at the onset of symptoms for 1 hour

Current Study: Ad Hoc Analysis in Patients With AF

- Some patients in NODE-303 experienced AF rather than PSVT; these episodes were the subject of this sub-study.
 - 21 of 1024 treated perceived-PSVT episodes (n = 18 patients) were actually AF/RVR rather than PSVT based on ECG data
 - Start of ECG recording was used as Time = 0 for assessment of ventricular rate (VR)

Results

- Mean VR \pm SEM = 129.7 \pm 5.4 bpm at baseline
- Of the 21 AF episodes analyzed, 17 had a VR \geq 110 bpm at baseline
 - Mean VR \pm SEM = 138.3 \pm 4.3 bpm
- 6 episodes converted to sinus rhythm over 60 min following etripamil administration
- Averaged reductions in VR from baseline were observed throughout the 60-min window
- Maximum reduction of -27.4 ± 6.1 bpm at 22 min, and -16.2 bpm \pm 5.6 at 60 min
- Etripamil was well-tolerated and there were no serious adverse events, including in 1 patient who self-administered 2 doses (separated by ~10 min)

Demographics and Results

	Patients With AF Episodes (n = 18)
Mean age, years	56.3
Female, %	56

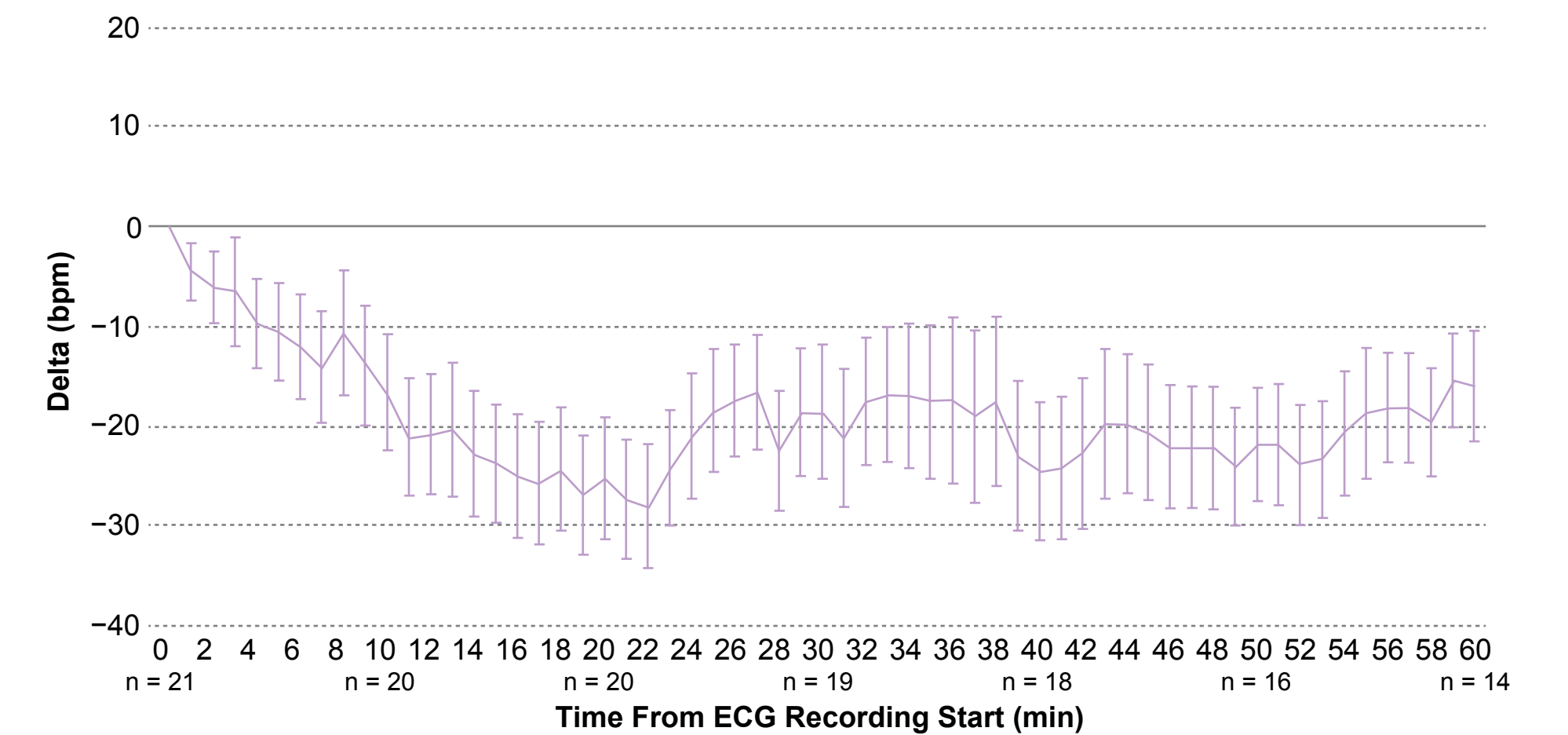
	BASELINE	15 MIN	30 MIN	45 MIN	60 MIN
AF ECGs used for analysis (NSR excluded)	21	20	19	17	14
Mean VR	129.7	104.6	110.7	103.9	110.2
SD	24.8	28.7	27.6	30	28.5
SEM	5.4	6.4	6.3	7.3	7.6
Median VR	127	95.5	108	98	114
Mean % change in VR from Baseline	0	-23.2	-18.4	-22.4	-16.2
SD	0	25.6	28	27.1	21
SEM	0	5.7	6.4	6.6	5.6
Median change in VR from Baseline	0	-28.5	-22	-25	-18

	Patients With AF Episodes (n = 18)
Patients with mild/moderate AEs related to drug, n (%)	7 (39)
Patients with severe AEs related to drug, n (%)	0 (0)

AE = adverse event; AF = atrial fibrillation; ECG = electrocardiogram; NSR = normal sinus rhythm; VR = ventricular response. The most frequent AEs include nasal congestion, nasal discomfort, and rhinorrhea.

Results

Change in Ventricular Response Rate From Baseline



Average difference \pm standard error from baseline in ventricular rate. The start of the ECG recording was used as an estimated dosing time for all episodes.

Conclusions

- In patients experiencing episodes of AF/RVR, self-administration of etripamil, an investigational new drug, resulted in a reduction in the VR that was sustained over 60 min
- Timing of response aligned with the known pharmacologic profile of etripamil nasal spray
- These findings warrant further study and suggest a potential role for the drug in the acute control of RVR in patients with AF

Limitations

- Time of drug administration was variably related to the start of ECG recording
 - Start time of the ECG recording was used as baseline for the analysis
- Patients have a history of SVT, and may not be representative of the entire AF population

ReVeRA-201 Trial

- Placebo-controlled, double-blind, single-dose study of etripamil in patients with AF and RVR
- In-hospital setting, drug given by medical staff, 3-channel Holter ECG recordings
- Currently ongoing in Canada and the Netherlands
- ClinicalTrials.gov NCT 04467905

References

1. Colilla S, et al. *Am J Cardiol.* 2013;112:1142-1147. 2. Go AS, et al. *JAMA.* 2001;285:2370-2375. Heart Rhythm 2023 | May 19-21, 2023 | New Orleans, LA