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LEADING ARTICLE

Etripamil Nasal Spray: Therapeutic Potential for Treating Paroxysmal Supraventricular Tachycardia

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Abstract
Patients with arrythmias are at an increased risk of heart-related comorbidities and complications. Specifically, patients with paroxysmal supraventricular tachycardia (PSVT), a type of arrythmia, are at increased risk of lightheadedness or shortness of breath, due to the increased rate of the heartbeat. Most patients are prescribed oral medications to control their heart rates and maintain a normal heart rhythm. Researchers have been tasked with discovering alternative treatment options with new delivery methods to treat arrythmias such as PSVT. A nasal spray was subsequently designed and is currently undergoing clinical studies. This review aims to present and discuss the current clinical and scientific evidence pertaining to etripamil.

Key Points

Etripamil offers a novel pathway for treatment of paroxysmal supraventricular tachycardia.

This mechanism is fast-acting without requiring invasive interventions.

1 Background

In the general population, supraventricular tachycardia, a group of arrhythmias, has a prevalence of 2.25 cases per 1,000 [1]. Paroxysmal supraventricular tachycardia (PSVT) is estimated to occur in 1 in 300 people in the USA [2]. PSVT is defined by a rapid heartbeat with an otherwise regular rhythm caused by a short circuit in the hearts' upper chamber [3]. Those at risk for arrythmias include patients with genetic dispositions, obesity, extreme endurance exercises, and excessive alcohol and tobacco consumption. Other common risk factors include coronary artery disease, hypertension, cardiomyopathies, and valvular heart disease [4]. Without proper treatment, complications can lead to myocardial infarction, angina, or even stroke. Current treatment options include calcium channel blockers (CCBs), which inhibit the L-type channels in humans, where contractility of the heart, the sinoatrial pacemaker, and atrioventricular conduction velocities are reduced [5]. Nonetheless, current oral medication options do not have a fast enough onset of action for patients experiencing symptoms. The rapid-onset treatment options available require invasive intravenous cannulation with extensive hospitalization. As a solution to these limitations, drug delivery via the pulmonary route with etripamil is being investigated to treat supraventricular tachycardia, primarily in young patients [6]. Etripamil results in an expeditious onset of action and efficient therapeutic benefit at low dosages. Compared with oral medications, pulmonary drug delivery averts first-pass metabolism and any associated toxicities typical of orally administered CCBs. In addition, the lungs' expansive surface area and thin vasculature for drug absorption allow for an efficient route for delivering etripamil to patients at a low dose without intensive and invasive care [4].

1.1 Mechanism of Action

Etripamil is a verapamil analog with the potential to treat cardiac arrythmias. It acts as a non-dihydropyridine L-type calcium channel blocker that enhances atrioventricular

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refractory periods while slowing nodal conduction. In comparison to other CCBs, which have a half-life of several hours, etripamil is short-acting with a half-life of 20 min, limiting the risk of potential complications that are associated with current long-term therapies used to treat PSVT. The greatest plasma concentration occurs at 8 min and the drug is metabolized by serum esterases in the blood, resulting in inactivation [7]. Additionally, etripamil has a shelf life of greater than 1 year [8].

1.2 Preclinical Pharmacology and Pharmacokinetics

Animal studies did not demonstrate prolongation of the QRS duration or corrected QT interval with use of etripamil [8]. Etripamil is delivered via nasal spray, allowing for faster absorption than similar treatments for PSVT [9]. It absorbs across the nasal mucosa and is fully utilized in the body in under 15 min, achieving an endpoint of cardioversion at this time [10]. The concentration plateaus at a 70 mg dose, as further drug delivery after this dose does not result in a higher effective concentration. Furthermore, etripamil is metabolized quickly by the body. Inactive carboxylic acid is the major metabolite of etripamil [9].

There is evidence to support that etripamil treats PSVT by altering atrioventricular nodal conduction via the slow wave pathway. This effect occurs approximately three minutes after inhalation. Etripamil has not been shown to affect the voltage in the coronary sinus region or the fast pathway region [11].

2 Clinical Studies

Stambler et al. conducted a phase II study to assess the safety and efficacy of etripamil nasal spray for the rapid termination of PSVT. During a pre-study visit, patients were randomly assigned to a study group in a 1:1:1:1:1 ratio: placebo or etripamil at 35, 70, 105, or 140 mg doses. The primary endpoint of this study was SVT conversion rate within 15 min of study drug administration. Secondary endpoints included time to conversion and occurrence of adverse effects. The study was performed during electrophysiological testing in patients with previously documented SVT who were induced into SVT prior to undergoing a catheter ablation. Induction of SVT was attempted using standard pacing and programming stimulation methods. A total of 104 patients were dosed, and conversion from SVT to sinus rhythm ranged 65%–95% in the etripamil nasal spray group and 35% in the placebo group. The differences were statistically significant, determined using a Pearson chi-squared test, in the three highest active compound dose groups versus placebo. In those patients who were converted, median time to conversion was less than 3 min. Adverse effects were related to the route of administration, resulting in local nasal irritation. Reductions in blood pressure occurred primarily in the highest etripamil dose. The safety and efficacy results from this study provide guidance for etripamil dose selection for future studies, particularly those involving self-administration in a real-world setting for the termination of PSVT, performed outside the electrophysiology laboratory in non-supine, non-sedated patients to confirm its efficacy. The observed balance between efficacy and safety in the 70 mg group provides support for this dose as a good candidate for future studies [8].

The NODE-301 study was a multicenter randomized double-blind placebo-controlled dose-ranging study that evaluated the effects of etripamil nasal spray in male and female patients 18 years and older. The NODE-301 study did not meet prespecified primary end point of PSVT conversion over five hours following the etripamil nasal spray 70 mg dose. Analysis at earlier timepoints demonstrated treatment effect during the first 30 min. This study served as a foundation for the RAPID study, which included a new dosing regimen involving up to two etripamil nasal spray 70 mg doses separated by 10 min [12].

The RAPID study is a two-part multicenter randomized double-blind placebo-controlled study that is evaluating the efficacy and safety of etripamil nasal spray to be self-administered by 701 patients who experience an episode of PSVT in an at-home setting. The RAPID study (NODE-301, part 2) describes the conduct of NODE-301 following the completion of part 1. The study enrolled patients were enrolled during part 1, but had not been dosed with the double-blind study drug or had not discontinued the study before the adjudication of the 150th positively adjudicated PSVT episode (15 January 2020). The RAPID study is composed of four arms, two of which consist of patients enrolled during part 1, randomized 2:1 to a single dose of study drug (etripamil nasal spray 70 mg or placebo) to treat a perceived episode of PSVT. The other two arms consist of newly enrolled patients who passed a test dose regimen of etripamil nasal spray 70 mg, randomized 1:1 to a dosing regimen of etripamil or placebo that allowed patients to self-administer a second dose to treat a perceived PSVT episode [13]. The RAPID study met its primary endpoint of adjudicated termination of a positively adjudicated episode of PSVT and conversion to sinus rhythm for at least 30 s within 30 min of start of study drug dosing, with 64.3% of those in the etripmail group versus 31.2% of those in the placebo group achieving the endpoint [14].

Furthermore, Ji Xing Pharmaceuticals is sponsoring a phase III multicenter randomized double-blind placebo-controlled study to determine whether etripamil nasal spray self-administered by Chinese patients is superior to placebo at terminating episodes of PSVT in an at-home setting. The safety and efficacy of etripamil nasal spray will be compared

Table 1 Ongoing and completed clinical studies of etripamil in patients with paroxysmal supraventricular tachycardia (PSVT)

Title	NCT Number	Phase	Intervention	Number of participants	Comments
Efficacy and safety of intranasal MSP-2017 (etripamil) for the conversion of PSVT to sinus rhythm (NODE-1) [8]	NCT02296190	II	Etripamil 35 mg, 70 mg, 105 mg, or 140 mg Placebo	199	Conversion from SVT to sinus rhythm ranged 65–95% in the etripamil group versus 35% with placebo The 70 mg dose was determined a good candidate for future studies
Efficacy and safety of etripamil for the termination of spontaneous PSVT (NODE 301 part 1) [12]	NCT03464019	III	Etripamil 70 mg Placebo	156	5-hour efficacy endpoint was not met Etripamil proved well-tolerated in a medically unsupervised setting
Efficacy and safety of etripamil for the termination of spontaneous PSVT. (NODE 301 part 2—The RAPID Study) [14]	NCT03464019	III	Etripamil 70 mg Placebo	701	Primary endpoint was met Etripamil demonstrated a higher rate of conversion to normal sinus rhythm within 30 min compared with placebo
Efficacy and safety study of etripamil nasal spray self-administration for the termination of spontaneous episodes of PSVT [13]	NCT05410860	III	Etripamil 70 mg Placebo	Estimated 500	Primary endpoint is time to adjudicated termination of a positively adjudicated episode of PSVT and conversion to sinus rhythm for at least 30 s within 30 min of starting study drug dosing Estimated completion date July 2024
Safety study of etripamil nasal spray for patients with PSVT (NODE-303) [17]	NCT04072835	III	Etripamil	1118	Open-label study where patients used etripamil when vagal maneuver was ineffective
Etripamil nasal spray in patients with PSVT [15]	NCT04952610	III	Etripamil Nasal Spray Bidose® System (Aptar Pharma)	200	Open-label extension for patients to have continued access to etripamil
Safety study of intranasal etripamil for the termination of spontaneous episodes of PSVT (NODE-302) [18]	NCT03635996	III	Etripamil Nasal Spray Bidose® System (Aptar Pharma)	169	Extension of NODE-301 to evaluate safety in the outpatient setting
Study of etripamil nasal spray in pediatric patients (NODE-202) [19]	NCT05763953	II	Etripamil	60	Not yet recruiting

with placebo on a range of clinical markers. The primary endpoint of the study is the time to adjudicated termination of a positively adjudicated episode of PSVT and conversion to sinus rhythm for at least 30 s within 30 min of starting study drug dosing. The study will include 500 randomized patients with an estimated completion date is July 2024 [14].

2.1 Safety

Across all treatment doses in the clinical phase II study, NODE-1, the incidence of all adverse events was not dose-dependent and was primarily associated with the intranasal route of administration. Common adverse events with incidence greater than 10% included nasal discomfort and congestion, rhinorrhea, oropharyngeal pain, increased lacrimation, cough, and nausea [8]. Of note, one study participant who received a 35 mg dose experienced shortness of breath, chest discomfort, and facial flushing, while another patient receiving the 105 mg dose experienced a cough, which was classified as a serious adverse event. One participant sustained second-degree atrioventricular block with hypotension following receipt of the highest dose (140 mg) and initial cardioversion to sinus rhythm. The block occurred 5 min after cardioversion and lasted for approximately 40 min before resolving. No adverse event resulted in either trial discontinuation or death, with most events related to local irritation and transient nasal congestion [9].

In the clinical phase III study, NODE-301, adverse events associated with the 70 mg dose were in line with the mild and transitory events identified in previous studies. Such events included nasal discomfort (19.6%), nasal congestion (8%), rhinorrhea (5.8%), oropharyngeal pain (5.1%), epistaxis (6.5%), headache (2.9%), sneezing (2.2%), dysgeusia (1.4%), and increased lacrimation (0.7%) [12].

In the phase III study NODE-303, patient self-administration of etripamil 70 mg nasal spray during episodes of PSVT after the failure of vagal maneuver to terminate the arrhythmia resulted in first degree atrioventricular heart block in two subjects, with otherwise no difference in safety between etripamil and placebo [8]. Etripamil has been designed as a short-acting agent with a favorable safety profile, making it a candidate for patient self-administration at home [8].

3 Discussion

Etripamil nasal spray is directed toward providing a self-administered shorting-acting treatment for patients with PSVT. Currently, the only available relief option is intravenous (IV) treatment with calcium or adenosine channel blockers administered in a professional medical setting. A medication for PSVT that can be self-administered would allow patients to treat symptoms and episodes without requiring a visit to the hospital. Episodic treatment may provide the additional benefit of allowing patients to halt chronic prophylactic therapy with beta blockers and CCBs [15]. The reduction of side effects and implications from these chronic medications may increase the quality of life for the patient [16]. Etripamil nasal spray allows for alternative options when the patient is considering serious treatment for their PSVT, such as an invasive catheter ablation procedure. While the results from the RAPID and NODE-301 studies are expected to fulfill the submissions requirements for the US Food and Drug Administrations (FDA) new drug application, ongoing studies will provide us with further information on the potential benefit of etripamil's short duration of action, contributing to the avoidance of long-term side effects, decreased patient visits to emergent medical centers for treatment, and increased efficacy of time to conversion along with confirmed safety and tolerability. Confirmed success in rapid conversion of PSVT episodes in an at-home setting are critical for etripamil. Additionally, etripamil is being studied for acute treatment of atrial fibrillation with rapid ventricular rate and other episodic conditions. See Table 1 for a list of ongoing and completed studies.

4 Conclusion

Etripamil offers a novel mechanism with a short half-life and administration that may alter the way patients with PSVT receive their treatment. To date, etripamil has demonstrated its value as a candidate for at home treatment for PSVT with a favorable safety profile. Etripamil is the first agent designed as a nasal spray and is undergoing evaluation to treat PSVT.

Declarations

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Conflict of interest Jessica Huston, Ariana Genovese, Andrea Ashchi, Amanda DeLuca, Jordyn Wiener, Elias Deeb, Alexander Deeb, and Rebecca F. Goldfaden declare that they have no potential conflicts of interest that might be relevant to the contents of this manuscript.

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Authors' contributions Jessica Huston was involved in supervision, data curation, analysis, reviewing, editing, and writing. Ariana Genovese was involved in data curation, analysis, and writing. Andrea Ashchi was involved in data curation, writing, and analysis. Amanda DeLuca was involved in data curation, analysis, and writing. Jordyn Wiener was involved in data curation, analysis, and writing. Elias Deeb was involved in data curation, analysis, and writing. Alexander Deeb was involved in data curation, analysis, and writing. Rebecca Goldfaden was involved in the conceptualization, project administration, reviewing, and editing.

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