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Fast Acting freedom: Intranasal Etripamil for sudden Paroxysmal Supraventricular Tachycardia

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ABSTRACT :

Patients with arrhythmias, such as Paroxysmal Supraventricular Tachycardia (PSVT), face a higher risk of heart-related issues and complications. PSVT can lead to symptoms like light-headedness, chest pain, anxiety, and shortness of breath due to the rapid heartbeat. To manage these symptoms, patients are typically prescribed oral medications to regulate heart rate and maintain normal rhythm. There is, however, a need for an effective PSVT treatment that is well-tolerated and can be self-administered with a rapid onset. Etripamil, a fast-acting L-type calcium channel blocker, is a non-dihydropyridine medication formulated as an intranasal spray to quickly terminate AV nodal-dependent PSVT episodes in situations where medical supervision is not available.

Key Words : PSVT, Etripamil, Safety, Nasal spray.

Introduction :

The prevalence of supraventricular tachycardia, a class of arrhythmias, in the general population is 2.25 cases per 1000 [1].Paroxysmal supraventricular tachycardia (PSVT) is thought to affect 1 in every 300 individuals in the United States [2]. Paroxysmal supraventricular tachycardia (PSVT) is characterized by a rapid heartbeat with a regular rhythm, caused by a short circuit in the upper chamber of heart [3]. If untreated, it can lead to serious complications such as myocardial infarction, angina, or stroke. Current treatments include calcium channel blockers (CCBs), which work by inhibiting L-type channels, reducing heart contractility, sinoatrial pacemaker activity, and atrioventricular conduction velocities [4]. However, oral medications available today don't act quickly enough for patients experiencing symptoms. Rapid-onset treatments typically require invasive intravenous procedures and lengthy hospital stays. To address these issues, research is exploring the use of etripamil delivered via the pulmonary route as a potential treatment for supraventricular tachycardia, especially in younger patients [5].

Etripamil : A new possible outpatient therapy for paroxysmal supraventricular tachycardia.

Etripamil is a verapamil analogue with potential for treating cardiac arrhythmias. It functions as a non-dihydropyridine L-type calcium channel blocker, enhancing atrioventricular refractory periods and slowing nodal conduction. Unlike other calcium channel blockers (CCBs) with long half-lives of several hours, etripamil has a short half-life of 20 minutes, reducing the risk of complications associated with current long-term PSVT treatments. The peak plasma concentration occurs at 8 minutes, and the drug is metabolized by serum esterase in the blood, leading to inactivation [6]. Its primary metabolite is an inactive carboxylic acid [7]. The combination of a convenient intranasal delivery method, rapid onset, and short half-life makes etripamil an appealing option for self-administration by patients outside of clinical settings [8].

Clinical studies :

In a Phase 1 study involving healthy volunteers, etripamil was administered Intranasally at doses ranging from 3.5 to 140 mg during sinus rhythm. The drug was quickly absorbed, reaching peak plasma concentration within 5 minutes of administration. Higher doses led to a dose-dependent increase in peak concentration and a greater extension of the PR interval [9]. All adverse events were mild, with no serious adverse events reported, and there was no observed prolongation of the QT interval [10]. All patients exhibited the expected pharmacodynamic effects with 70 mg etripamil for PSVT, as demonstrated by a PR interval prolongation on the ECG lasting approximately 5 to 50 minutes [11]. In a Phase 2, double-blind, parallel-design study, 104 randomized patients were administered etripamil at doses ranging from 35 to 140 mg or a placebo during episodes of atrioventricular nodal–dependent SVT induced in an electrophysiology laboratory. In this study, after at least 5 minutes of sustained arrhythmia, participants received the study drug

Intranasally, with the goal of achieving cardioversion within 15 minutes of administration. The doses tested were placebo, 35 mg, 70 mg, 105 mg, and 140 mg, with 35%, 65%, 87%, 75%, and 95% of patients reaching the desired endpoint, respectively. The differences between the active doses and the placebo were statistically significant, as determined by a Pearson chi-squared test, for the three highest doses. For patients who achieved conversion, the median time to conversion was under 3 minutes. Adverse effects were mainly related to the administration method, causing local nasal irritation, while reductions in blood pressure were most pronounced at the highest dose of etripamil. The study's safety and efficacy results offer guidance for selecting the appropriate etripamil dose for future research, especially in real-world settings where patients self-administer the drug outside of clinical environments. The 70 mg dose showed a favourable balance between effectiveness and safety, making it a promising candidate for future studies [12].

The main goal of this phase 3 study was to assess whether self-administering a 70-mg nasal spray of etripamil is more effective than a placebo in terminating PSVT. This was evaluated by both the percentage of patients who achieved sinus rhythm and the time taken to achieve conversion to sinus rhythm, within a 5-hour observation period [13]. Ji Xing Pharmaceuticals is sponsoring a phase 3, multicentre, randomized, double-blind, placebo-controlled study to evaluate whether etripamil nasal spray, self-administered by Chinese patients, is more effective than a placebo in terminating PSVT episodes in a home setting. The study will compare the safety and efficacy of etripamil nasal spray with placebo across various clinical markers [14].

Safety of Etripamil :

In the Phase II clinical study, NODE-1, the frequency of all adverse events was not related to the treatment dose and was mainly linked to the intranasal administration method. Common side effects occurring in more than 10% of participants included nasal discomfort and congestion, runny nose, sore throat, increased tear production, coughing, and nausea [12]. Notably, one participant who received a 35 mg dose experienced shortness of breath, chest discomfort, and facial flushing, while another receiving the 105 mg dose developed a cough, which was classified as a serious adverse event. A participant who received the highest dose of 140 mg experienced second-degree atrioventricular block with hypotension after initial cardioversion to sinus rhythm. The block occurred 5 minutes post-cardioversion and lasted around 40 minutes before resolving. No adverse events led to discontinuation of the trial or death, with most events being related to local irritation and temporary nasal congestion [15]. In the Phase III clinical study, NODE-301, the adverse events linked to the 70 mg dose were consistent with the mild and temporary events observed in earlier studies. These included nasal discomfort (19.6%), nasal congestion (8%), runny nose (5.8%), sore throat (5.1%), nosebleed (6.5%), headache (2.9%), sneezing (2.2%), altered taste (1.4%), and increased tear production (0.7%) [13]. In the Phase III NODE-303 study, patients who self-administered 70 mg of etripamil nasal spray during PSVT episodes, after a failed vagal maneuver to stop the arrhythmia, experienced first-degree atrioventricular heart block in two individuals. Otherwise, there was no significant difference in safety between etripamil and placebo. Etripamil was developed as a short-acting drug with a favourable safety profile, positioning it as a potential option for patients to administer themselves at home [12].

Discussion :

Etripamil nasal spray is designed to offer a self-administered, short-acting treatment for patients with PSVT. Currently, the only treatment option available is intravenous (IV) administration of calcium or adenosine channel blockers in a clinical setting. A self-administered medication for PSVT would enable patients to manage symptoms and episodes without needing a hospital visit. Additionally, episodic treatment could allow patients to discontinue long-term prophylactic therapy with beta blockers and calcium channel blockers (CCBs) [16]. Reducing the side effects and impact of these long-term medications could improve the patient's quality of life [17]. Etripamil nasal spray offers an alternative option for patients considering more invasive treatments for their PSVT, such as catheter ablation. While the results from the RAPID and NODE-301 studies are expected to meet the submission requirements for the US FDA's new drug application, ongoing studies will provide additional insights into the benefits of etripamil's short duration of action. This may help avoid long-term side effects, reduce patient visits to emergency medical centres, and improve the time to conversion, along with confirming its safety and tolerability. Demonstrated success in rapidly converting PSVT episodes in a home setting is crucial for etripamil. Additionally, etripamil is being investigated for the acute treatment of atrial fibrillation with rapid ventricular rate and other episodic conditions.

Conclusion :

Etripamil presents a unique mechanism of action with a short half-life and method of administration that could change how patients with PSVT are treated. So far, etripamil has proven to be a promising option for at-home treatment of PSVT, with a favourable safety profile. It is the first nasal spray specifically developed for treating PSVT and is currently being evaluated for this purpose.

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