**The efficacy of Vernakalant, an atrial selective fibrillating agent**

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**Abstract**

An arrhythmia is a disturbance in the rate or rhythm of a normal heartbeat. It indicates that the heart is beating too fast, too slowly, or unevenly. Atrial fibrillation is the most frequent arrhythmia that can lead to blood clotting, which may cause cardiac and related complications. Medication, therapy to reset the heart rhythm, and catheter operations to block incorrect heart signals are all possible treatments for atrial fibrillation. Intravenous Vernakalant is successful regardless of sex, age, or rate of rhythm control treatment usage. It is a safe and well-tolerated medication for patients suffering from atrial fibrillation. In individuals with a history of ischemic heart disease, it also provides a successful treatment option for converting Atrial fibrillation with an acceptable safety profile. Vernakalant was faster than placebo, Amiodarone, propafenone, and flecainide at converting recent-onset atrial fibrillation to sinus rhythm. Therefore, it is recommended as a therapy of choice based on clinical trials with real-world evidence.

**Keywords: V**ernakalant, Atrial fibrillation, Atrial selective agonist, RSD1235.

**Introduction**

It was one hundred years; Willem Einthoven reported the electrocardiogram showing atrial fibrillation (AF) in 1906, which affects a minimum of 1-2% of the world's population (1). Its effect develops with age, such as 5% of people developing AF at age 65, which increases to 8% when the generation reaches seventy-five. Patients with various stages of AF are treated or managed with different modules, including rate or rhythm control. Preliminary AF treatments were always considered either electrical cardioversion or a pharmacological agent to facilitate chemical cardioversion. This treatment was observed in 41 countries across the globe under the European Society of Cardiology umbrella in 2016 with a new promising ligand, RSD1235 (2).

RSD1235, later coined as Vernakalant, amino cyclohexyl ether, comes under AF-converting agents that produce significant action on the heart's upper chamber and non-significant effects on the lower section of the heart. Vernakalant is the marked antiarrhythmic drug of choice for atrial tissue, which affects the refractory period of the atria, but has minimum effect on ventricles. Vernakalant is designed for rapid termination of acute onset AF in patients with no or minimal heart disease and some forms of structural heart disease, including stable coronary heart disease, left ventricular hypertrophy, or mild heart failure. Previous reports and its critical assessments documented that Vernakalant is a promising agent for the selective treatment of AF. This review will remind researchers to consider Vernakalant as an antiarrhythmic agent for future perspective in the broader population (3).

Vernakalant is a rapid-acting, relatively atrial-selective antiarrhythmic drug approved in Canada and Europe for the pharmacological cardioversion of recent-onset Atrial fibrillation. Vernakalant, amino cyclohexyl ether, is a type of AF-converting drug that significantly affects the heart's upper chamber and has negligible impact on the lower section. Vernakalant, which affects the refractory period of the atria but has little effect on the ventricles, is the preferred marked antiarrhythmic medication for atrial tissue. Vernakalant is intended for persons with no or minimal heart disease and some types of structural heart disease, such as stable coronary heart disease, left ventricular hypertrophy, or mild heart failure, to rapidly terminate acute onset AF. According to prior studies and critical evaluations, Vernakalant is a potential drug for the targeted therapy of AF. This assessment will remind scientists to consider Vernakalant as an antiarrhythmic drug in the future (3). Considering that recent-onset symptomatic AF resolves spontaneously within 24 hours in more than 70% of cases, it may be best to wait and see with rate control medication for patients in the emergency room who have recently developed the condition. In addition, the 2016 European Society of Cardiology (ESC) Guidelines advised that rhythm control should be considered in patients who continue to experience symptoms despite the rate control method. There is a clinical tendency. Nonetheless, that rhythm control is preferable to stop atrial remodelling and the development of paroxysmal or persistent AF into permanent AF. Electrical or pharmaceutical cardioversion can be used to control rhythm; the choice depends on the physician's preference and may be influenced by prior knowledge, regional customs, and legal requirements. In particular, where there is no hemodynamic compromise, pharmaceutical cardioversion is chosen as a first-line strategy in patients who tolerate their arrhythmia. Pharmacological cardioversion has the benefit of not requiring general anaesthesia or conscious sedation while the patient is fasting, as well as perhaps having less psychological effects than electrical cardioversion and possibly having a lower risk of immediate recurrence; The more muscular antiarrhythmic drug (AAD) loading often used in pharmacological cardioversion, which provides a significant efficacy immediately and for the hours and days following cardioversion, is probably connected to the lower chance of an immediate recurrence. Whether the "pill-in-the-pocket" pharmacological treatment (Flecainide, Propafenone, and Sotalol) can end paroxysmal AF quickly is debatable. The situation's urgency influences the "pill-in-the-pocket" technique's use and effectiveness, the patient's cooperation, the doctor's experience, the drug's availability, any underlying heart conditions, and other factors. There is insufficient data to advocate the "pill-in-the-pocket" approach for treating patients with paroxysmal AF. Furthermore, many AADs (such as amiodarone and beta-blockers) have a sluggish beginning of the action in paroxysmal AF or may have some limitations for usage in patients with underlying cardiac disease (class 1 AAD). As a result, it was sought after to create innovative and efficient AAD to treat patients with paroxysmal AF.

**Chemistry of Vernakalant**

***Chemical name and properties***

Chemically vernakalant is also known as “(1R,2R)-2-[(3R)-hydroxypyrrolidinyl]-1-(3,4-dimethoxyphenethoxy) cyclohexane monohydrochloride, With a chemical formula of C20H31NO4.HCl. The basic moiety of Vernakalant belongs to the cyclic class imides with three chiral centres(4).

***Synthesis***

Vernakalant hydrochloride is made primarily by chemical synthesis over a five-step procedure that guarantees the chirality of every chiral centre. As a result, a single polymorphism pathway produces the anhydrous, non-solvated substance.

This method yields 56% overall yield by three new transformations, comprising a ZnCl2 and pyrrolidine-mediated -etherification, an enzymatic versatile asymmetric transamination (DA-TA) of a -substituted ketone, and an alkyl-B(OH)2-mediated amidation(5).[Fig:2,3]



Fig-1: Asymmetric transamination (DA-TA) of a -substituted ketone



Fig-2: ZnCl2 and pyrrolidine-mediated -etherification and an alkyl-B(OH)2-mediated amidation

Recently another method has been developed with Ammonium persulfate–dimethyl sulfoxide (APS–DMSO), a new dehydrating agent for a simple one-pot procedure that produces high yields of various cyclic imides from primary amines and cyclic anhydrides which are widely available(4).[Fig:1]



Fig 3: Synthesis of vernakalant with the help of Ammonium persulfate–dimethyl sulfoxide

***The Chemistry Behind Vernakalant's High-Affinity Association***

A recent study of Vernakalant's molecular aspects of interaction with the Kv1.5 channel's inner pore is compared to the interactions of the category IC compound flecainide, which shows that Vernakalant effectively inhibits channels that have been triggered and leave the interior vestibule as the track closes. The molecular docking study of Vernakalant binding mechanisms to the open state of the Kv1.5 channel structure could be explored through modelling utilising AutoDock4. The most convenient conformation had a free energy of binding (FEB) of 7.12 kcal/mol and an estimated Ki of 6.08 mM (actual IC50 for Vernakalant is 13.8 mM). This conformation appears specifically designed to restrict the channel pore as it interacts with all four T480 residues(2).

***Mode of action***

Vernakalant modestly inhibits Ito, IK.ATP, IKr, and late INa currents are expressed in the ventricles, characterising them as "Atrial selective." It shows higher sensitivity for atria-specific IKur over other channels involved in ventricular repolarisation, such as IKr and INa, which is mainly responsible for its safety(6). Vernakalant blocks sodium channels, and this action varies with heart rate and membrane potential. Vernakalant is a mild activator of the sodium channel blocker at low heart rates and negative membrane resting potentials (INa). Due to Vernakalant's increased affinity for INa, as the heart rate rises, there is a more pronounced INa blockage, and the medicine starts to work quickly. Additionally, Vernakalant has a quick offset of binding, which is highly desirable in an antiarrhythmic medication after the heart rate lowers and the INa blockage is no longer necessary. State-dependent INa blockage may be the basis for Vernakalant's AF-selective activities. However, Vernakalant's effect on late INa current is frequency-dependent with fast offset kinetics, which means that blockage of this current and slowing of atrial conduction are more noticeable at higher atrial rates. Vernakalant is ideal for treating rapid atrial fibrillation or other atrial tachyarrhythmias. Furthermore, further data support the idea that Vernakalant exhibits a ranolazine-like antiarrhythmic activity by late INa current reduction, inhibiting drug-induced proarrhythmic from dofetilide and acting as a protective factor for the ventricular myocardium.

Normal atria have a resting membrane potential between -70 and -80 mV, roughly ten mV more positive than the ventricles. The discrepancy between the atria and ventricles' resting membrane potentials rises in AF as the atria fail to repolarise fully. It is theorised that Vernakalant selectively blocks sodium channels in the diseased tissue and atria rather than the healthy ventricles because of this increased disparity in membrane potential. However, Vernakalant's mode of action greatly emphasises its capacity to block particular potassium channels. It inhibits the potassium current IKur, which is involved in atrial repolarisation repolarization-selective. Additionally, Vernakalant blocks the second atrial-selective potassium channel, IKACh, at low concentrations, lengthening the atrial action potential duration and extending the plateau(7).

**Table 1:** Action potential in Atria and ventricular myocardium.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Current** | **Gene** | **The phase of action potential** | **Ion direction** | **Atria** | **Ventricles** |
| INa | hH1 | o | Inward | + | + |
| ICa, L, T | SCN5A | 2 | Inward | + | + |
| Ito | Kv4.2/4.3 | 1 | Inward | + | + |
| IKs | KCNQ1 | 3 | Outward | + | + |
| I Kr | HERG | 2,3 | Outward | + | + |
| IKur | KV1.5 | 2,3 | Outward | + | - |
| ICl | CTRF/TWIK | 2,3 | Outward | + | + |
| Ik1 | Kir 2 family | late 3& 4 family | Outward | + | + |
| Ik.ATP/Ach | Kir3 family | late 3& 4 family | Outward | + | ­- |

***Electrophysiological &hemodynamic effects***

The mean QRS interval ↑increased, Transient prolongations of the QTc interval, and QTcF interval prolongations of at least 30 milliseconds. The mean Bazett-corrected QT interval (QTcB) ↓, monomorphic unsustained ventricular tachycardia (VT), and Ventricular extrasystoles decreased. Reduced mean heart rate from baseline (mean 106 beats/min) occurred in intravenous (IV) vernakalant patients. In the 24 hours from drug infusion, hypotension was reported in vernakalant patients. Among those given Vernakalant, WHO remained in AF or atrial flutter (AFL), the decrease in heart rate (HR), Any hr< 40 beats/min on Holter (1.7%). Any hypotension event (2.2%) systolic blood pressure (SBP) < 90 mm Hg (1.3%)(8).

***Pharmacokinetics profile***

Intravenous Vernakalant was effective regardless of sex, age, rate, rhythm control therapy and medical history, including congestive heart failure, myocardial infarction, hypertension, ischemic heart disease, renal impairment, and hepatic impairment. However, intravenous Vernakalant should be used cautiously in hemodynamically stable patients with New York Heart Association (NYHA) class I or II congestive heart failure (CHF) and is contraindicated in patients with NYHA class III or IV CHF(7).

Age, sex, liver, and renal function do not impact the pharmacokinetic properties of Vernakalant Orally administered, and Vernakalant is transported in the systemic circulation and distributed within 30 mins. It remarked a very short half-life and is metabolised primarily by the hepatic cytochrome P-450 (CYP) 2D6 (CYP2D6) system and excreted within 2 to 5 hours. Oral Vernakalant prescribed doses are 150, 300, 500, and 600 mg/kg twice daily. No episodes of torsade de pointes found in the previous activities. The adequate formulation of Vernakalant is intravenous, recommended in an environment where continuous cardiac monitoring is available, initially at 3 mg/ kg over 10 min. If the sinus rhythm is not restored within 15 min following the end of the first infusion, a second 10 min infusion of 2 mg/kg can be administered. Vernakalant is rapidly and extensively distributed into tissue & saliva. Protein binding was low for Vernakalant (25-50%). Blood: Plasma concentration ratios were generally less than one, indicating that Vernakalant does not explicitly bind to erythrocytes. The free fraction of Vernakalant is 53-63% in human serum (EMA). Patients are categorised as weak (half-life of 5.6 hours) or extensive metabolisers based on the plasma half-life, dependent on CYP2D6 activity (2.2 hours). The maximum plasma concentration, the area under the plasma concentration curve, is 3.29 mcg/ml, 11.64 mcg.Hr/ml in men and 4.57 mcg/ml, 11.64 mcg.Hr/ml in a woman. The primary inactive metabolite of this substance, RSD1385, is primarily dependent on 4-O-methylation by the cytochrome P-450 (CYP) 2D6 isoenzyme and fast glucuronidation. Excretion of Vernakalant is taken place in the liver and kidney. Therefore, 11% of the unchanged drug is eliminated in the urine(9).

Oral / IV, Absorbed by the bloodstream

Absorption

Distribution phase is 30 min, rapidly and extensively distributed into tissue, maximum plasma concentration time is 10-minute, average plasma half-life is 3.1 hours in men and 2.9 hours in women, the average maximum plasma concentration (Cmax) is unaffected by CYP2D6 genotype and is 3.29 μg/mL in men and 4.57 μg/ mL in women. Vernakalant half-life (*t*½) is between 2 and 4 h, the area under curve (AUC) between 0 and 90 min

Distribution

Metabolism

Metabolized by cytochrome P450 (CYP) 2D6-mediated O-demethylation, followed by rapid glucuronidation and to a lesser extent by direct glucuronidation. Its major inactive metabolite, RSD1385, is predominantly dependent on 4-O-methylation by cytochrome P-450 (CYP) 2D6 isoenzyme. Plasma half-life is dependent on CYP2D6 activity classifying patients as poor (half-life 5)

Excretion

Vernakalant is cleared both by the liver and the kidney. Elimination half-life is found to be 3.1 hour in men and 2.9 hour in women. 11% of the drug is secreted unchanged in the urine

Fig. 4: Pharmacokinetic study of vernakalant

***Preclinical trials***

Vernakalant was employed in a rabbit model of acquired Short QT syndrome (SQTS). The ATP-sensitive K channels in the heart are opened by injecting 1µM pinacidil. This shortens the action potential duration (APD) and QT intervals and increases the likelihood of arrhythmias (ventricular fibrillation) brought on by planned stimulations. Vernakalant reduced ventricular fibrillation while extending the APD and QT interval. Vernakalant hasn't been studied on SQTS patients or SQTS cardiomyocytes, though. The potassium voltage-gated channel subfamily H member 2 (KCNH2) gene mutation N588K, which has been identified as the pathogenic mutation for SQTS1 in previous research, has been identified as the APD-prolonging and antiarrhythmic effects of Vernakalant in human induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs) from a patient with SQTS1. These cells are known as SQTS1-hiPSC-CMs. Vernakalant dramatically altered the action potential (APs), primarily the Vmax, APD50, and APD90, in the SQTS1-hiPSC-CMs. Since peak sodium channel currents are a significant determinant of Vmax in cardiomyocytes, the decrease in Vmax is consistent with its Na channel-blocking effect. However, how Vernakalant prolonged, the APD in SQTS1-hiPSC-CMs needs to be clarified(10).

***Clinical trials***

1. In the AVRO (amiodarone in subjects with recent onset atrial fibrillation) trials, intravenous Vernakalant reported better efficacy than Amiodarone for speedy conversion of recent-onset Atrial Fibrillation. The main objective was for patients with sinus rhythm 90 minutes after starting therapy. As a result, treatment with Vernakalant altered 51.7% of patients to sinus rhythm at 90 minutes compared with 5.2% of patients treated with Amiodarone with a median time of conversion of 11 min; moreover, there were no significant side effects. Also, there were no cases of ventricular arrhythmia(11).

2. The study aimed to ascertain the safety and efficacy of Vernakalant, a multi-channel blocking agent, in combination with external electrical cardioversion in patients with recent-onset (≤7-day) AF. After the initial dose of Vernakalant, conversion to sinus rhythm (SR) could be accomplished in 55% of instances. Only 167 individuals (73%) could have their sinus rhythm restored by medication within a median of 11 minutes (IQR 8-29). After the initial dose of Vernakalant, conversion to SR could be accomplished in 55% of instances. Only 167 individuals (73%) could have their sinus rhythm restored by medication within a median of 11 minutes (IQR 8-29). Within 196 minutes (IQR = 149-300) of the first dose of Vernakalant, Electrical cardioversion was accomplished on 62 of the remaining 63 pharmacological non-responders yielding a total success rate of 99%. No immediate atrial fibrillation (IRAF) reinitiation was observed in any patients undergoing electrical cardioversion. No severe rhythm disorders such as torsade de pointes tachycardia, ventricular fibrillation, polymorphic or sustained/non-sustained VT, and premature ventricular contractions (PVC) could be observed during and after Vernakalant treatment. However, recent-onset atrial flutter was recorded in 31 (14%) patients as a minor adverse event(11).

3. In this CRAFT (Canadian remote access framework for clinical trial) trial, RSD 1235, a novel antiarrhythmic agent, was studied to treat recent-onset atrial fibrillation. The treating physician, patient, treating nurse, research nurse, family physician, follow-up evaluation, and outcome adjudicators were all subjected to multiple blinding layers. Patients were randomized into three groups' high dose (RSD2), low dose (RSD1), and placebo. After the first infusion, the primary endpoint was 61% of the patient's high amount RSD2 infusion, 11% low dose RSD1, and 5% after placebo + placebo—statistically significant difference (p < 0.0005) between placebo and the RSD-2 groups. The median time to terminate AF was 11 minutes after the first infusion in the RSD2 group, which was adequate. The percentage of patients with sinus rhythm, excluding those electrically cardioverted at 30 min after information, was 56% in the RSD-2 group, 11% in the RSD-1 group, and 5% in the placebo group. At one hour and 24 hours, 53% and 79% of patients in the RSD-2 group had sinus rhythm, compared to 11% and 56% in the RSD-1 group and 5% and 45% in the placebo group. The median time to conversion to sinus rhythm during the 24-h observation period (excluding those electrically cardioverted) from the start of the first infusion in the RSD-2 group was 14 min, p= 0.016 vs. placebo). The RSD-1 group's median time to conversion to sinus rhythm was 166 min, with a p-value of 0.886 compared to the placebo. Significantly prolong the QTc or QRS intervals, as compared with placebo. There was no difference in the QT and QTc intervals between the placebo (389+31 ms vs. 414+16 ms) and RSD-2 treatment (366+28 ms vs. 42719 ms). There were no significant fundamental changes in systolic blood pressure. Clinically significant treatment-related decreases in mean heart rate from baseline (mean 106 beats/ min) occurred in patients administered the RSD-2 dose. Paresthesia, nausea, and hypotension were the adverse effects reported during the study from RSD. Everyday adverse events experienced in this study were cardiac disorders, reported by 35.0% in the placebo group, 22.2% in the RSD-1 group, and 16.7% in the RSD-2 group. One patient in the RSD-1 group experienced ventricular fibrillation. Within the study period (24 h), electrical cardioversion was successful in 89% of 20 placebo-treated, 100% RSD-1-treated, and 100% RSD-2–treated patients (12).

4. This Phase 3 study involved randomized, placebo-controlled trials. Vernakalant hydrochloride's effectiveness for short-term (less than seven days) and long-term (8 to 45 days) atrial fibrillation conversion has been evaluated (long duration). Patients with AF lasting 3 to 48 hours with Vernakalant confirmed the highest adaptation rate (62.1% versus 4.9% with placebo; P<0.001). In the primary efficacy investigation, Vernakalant patients with short-duration AF (3 hours to 7 days) converted to sinus rhythm within 90 minutes, compared to 3 of 75 placebo patients (4.0%; P<0.001). The median time to sinus rhythm conversion for the Vernakalant group was 11 minutes. Overall, 83 of the 221 Vernakalant patients (37.6%) had their AF terminated, compared to 3 of the 115 placebo patients (2.6%; P<0.001). During the initial 90 minutes, 19 Vernakalant patients (8.6%) experienced atrial flutter, with five converting to sinus rhythm. During the first 24 hours after infusion, there were no reports of torsade de pointes or ventricular fibrillation. There were 21 placebo patients (18.3%) and 29 Vernakalant patients (13.1%) who required hospitalisation due to serious adverse events of cardiac origin (placebo, 12.2%; Vernakalant, 5.9%). Hypotension was reported as an adverse event in 14 Vernakalant patients (6.3%) and four placebo patients (3.5%) (13).

5. The purpose of this phase 3 prospective, randomised, double-blind, this placebo-controlled study was to determine the efficacy and safety of Vernakalant Hydrochloride for the Rapid Conversion of Atrial Fibrillation following cardiac surgery. As a result, 161 coronary artery bypass surgery (CABG) patients (54 placebos and 107 Vernakalant) were treated and included in the efficacy and safety analyses. Conversion of AF/AFL to SR for a minimum of 1 minute within 90 minutes of the first infusion was achieved in 44.9% (48 of 107) and 14.8% (8 of 54) of patients given Vernakalant and placebo, respectively (P<0.001). In patients with AFL at baseline, none of the Vernakalant patients converted to SR. In patients who had CABG surgery alone, there was a significant difference in responder rates between Vernakalant and placebo (34/71 [47.9%] versus 5/37 [13.5%], P=0.002). There was no effect of age, gender, left ventricular ejection fraction (LVEF), or left atrial diastolic dimension on the likelihood of conversion to SR. The median time to conversion for AF-to-SR transformation with Vernakalant was 12.4 minutes. The median time to conversion was 12.3 minutes among AF/AFL patients who responded to Vernakalant treatment (0.5 to 57.1 minutes). In the first 2 hours and 24 hours after beginning dosing, four patients received Vernakalant and witnessed nonsustained ventricular tachycardia lasting 3 to 12 beats. Bradycardia happened more frequently in the Vernakalant group. The SBP in Vernakalant patients was 90 mm Hg. There were no cases of torsade de pointes, sustained ventricular tachycardia, or ventricular fibrillation in either treatment group (14).

6. In the cardiovascular emergency care division, this study compared the conversion times of recently developed AF in hemodynamically healthy individuals deprived of structural heart ailment who received either intravenous Vernakalant or oral propafenone treatment. Each patient exhibited hemodynamic stability, symptomatic recent-onset AF (lasting less than 48 hours), and no structural heart abnormalities. In the propafenone group, there were 19 patients, while in the vernakalant group, there were 17 patients. In the Vernakalant group, sinus rhythm conversion took 9 minutes, whereas it took 166 minutes in the propafenone group (P=0.0001). As a result, 7% of patients in the Vernakalant group and 22% in the propafenone group required electrical cardioversion (ECV). Hospital stay was 43% shorter in the Vernakalant group (P=0.0001).In the Vernakalant group, 47% of patients experienced adverse events, compared to 5% in the propafenone group. Only one patient in each group experienced a severe adverse event: bradycardia lasting less than five minutes in both groups at a rate of 40 beats per minute. Coughing fits, and transient dysgeusia was frequent in the Vernakalant group. There were no late adverse events reported (15).

7. These arrhythmia conversion trials I (ACT I) and ACT IV were multinational, multicenter, phase 3 clinical trials. The study sought to evaluate the efficacy and safety of Vernakalant for patients with recent-onset AF. The population for this analysis is the subgroup of 290 patients with AF lasting > 3 to ≤48 hours, including 229 given Vernakalant (99 in ACT I and 130 in ACT IV) and 61 given placebos (in ACT I). Two hundred twenty-nine patients with recent-onset AF treated with Vernakalant, 136 (59.4%; 95% confidence interval [CI] = 53% to 66%) converted to sinus rhythm within 90 minutes, compared with 3 (4.9%; 95% CI = 1% to 14%) of the 61 patients given placebo (p< 0.0001). The median time to conversion with Vernakalant was 12 minutes. Between 2 and 24 hours, 33.6% of all Vernakalant patients received ECV and other AAD, compared to 80.3% of all placebo patients. Among no responders (patients who did not convert in 90 minutes), 59.1% of the 93 patients in the Vernakalant group received ECV or AADs between 2 and 24 hours, compared to 84.5% of the 58 no responders in the placebo group. In the first 2 hours of study drug administration, seven patients (3.1%) experienced severe AEs in the Vernakalant group, primarily events of Bradycardia and hypotension, compared to no patients in the placebo group. From 2 to 24 hours after drug administration, the most common AEs dysgeusia (weird taste), sneezing, paresthesia, nausea, pruritus, and cough. Reports showed that the incidence of ventricular arrhythmia, Bradycardia, and hypotension was similar in the placebo and Vernakalant-treated patients. There were no cases of torsade de pointes, ventricular fibrillation, or sustained ventricular tachycardia (VT) (16).

8. Vernakalant hydrochloride was tested in this Phase 3 Randomized Controlled Trial for Cardioversion of Recent-onset Atrial Fibrillation to determine its safety and effectiveness in converting symptomatic recent-onset AF in patients to SR. Vernakalant was chosen for this trial at 35 sites in Korea, Taiwan, and India (n = 55 for Vernakalant; n = 56 for placebo). In the 90 minutes following the initial medication exposure, a statistically substantially higher percentage of patients in the Vernakalant group than in the placebo group switched from AF to SR for at least one minute [52.7% (29 of 55) vs. 12.5% (7 of 56), respectively; p< 0.001]. Additionally, the time to cardioversion was substantially quicker in the Vernakalant group than in the placebo group (P<0.001) in the first 90 minutes following the infusion. In the Vernakalant group, the median time to conversion was 11.0 minutes (n=29), while it took 19.2 minutes (n=7) in the placebo group. Within 24 hours, the conversion rate versus placebo improved by 32% relative and 15% absolute, taking electrical cardioversion patients into account as no responders. The Vernakalant and placebo groups were comparable regarding the frequency of treatment-emergent adverse events (TEAEs) like VT, Bradycardia, sinus arrest, sneezing, dyspnea, and dysgeusia. Each group had six patients who reported dyspnea as an SAE. Vernakalant was linked to momentary prolongations of the QTc and QTcF intervals compared to placebo(17).

9. The effectiveness of vernakalant hydrochloride (RSD1235) in treating atrial fibrillation (AF) for lengths of 3 hours to 7 days (short duration) and 8 to 45 days was investigated in this Phase 3 prospective, randomised, double-masked study (long-term).In the group of patients with short-lasting AF, 90 minutes later, 75 of the 145 Vernakalant patients (51.7%) had switched to sinus rhythm, compared to 3 of the 75 placebo patients (4.0%; P<0.001). (3 hours to 7 days). The most considerable conversion rate was seen in patients taking Vernakalant for AF, lasting 3 to 48 hours (62.1% vs. 4.9% with placebo; P< 0.001). The change to sinus rhythm took the 75 Vernakalant patients an average of 11 minutes. 19 Vernakalant patients (8.6%) had an atrial flutter in the first 90 minutes; 5 later switched to sinus rhythm. These atrial flutter episodes were not of them connected to 1:1 atrioventricular conduction. All three of the patients who died had taken. Vernakalant. Neither of these deaths was thought to be the result of research medications. Severe side effects were reported in 29 Vernakalant patients (13.1%) and 21 placebo patients (18.3%). Most incidents involved the heart, with hospitalisation for recurrent AF being the most common (placebo, 12.2%; Vernakalant, 5.9%). Within the first 24 hours, patients taking Vernakalant reported dysgeusia (29.9% Vernakalant, 0.9% placebo), sneezing (16.3% Vernakalant, 0% placebo), paresthesia (10.9% Vernakalant, 0% placebo), nausea (9.0% Vernakalant, 0.9% placebo), and hypotension (6.3% Vernakalant, 3.5% placebo). There were no reports of torsade de pointes or ventricular fibrillation during the first 24 hours after infusion. Vernakalant had no discernible hemodynamic effects on mean systolic or diastolic blood pressure. In the 24 hours following the onset of the medication infusion, 14 Vernakalant patients (6.3%) and four placebo patients (3.5%) experienced hypotension(17).

10. The study analysed the predictors of conversion in 2-years of experience using intravenous Vernakalant to treat recent-onset atrial fibrillation. One hundred twenty-one consecutive patients treated with Vernakalant were included. Hypertension was present in 46.4% of the patients, and only 1.8% had diabetes. Structural heart disease was present in 13.4% of patients, with an average ejection fraction of 60.2 ± 6.4 and a left atrial area of 20.6 ± 4.4. Conversion to sinus rhythm was achieved in 84.5% of patients, and 46% required the second dose of Vernakalant. The time to conversion was 10 minutes. Structural heart disease was significantly greater in the group without modification (35.3 vs. 9.7%; P=0.02. The mean EF in the group with conversion was 61.05± 5.7% versus 54.9±8.4% in the group without conversion (P=0.016); patients with EF *<*55% had a lower conversion rate(15).

11. To safely and quickly restore sinus rhythm and promote same-day discharge, the study examined the viability of chemical cardioversion of recently developed atrial fibrillation in the emergency room using vernakalant hydrochloride. With a mean age of 57.7 years (32-82) and a male preponderance of 76.2%, consecutive patients with non-valvular AF in our emergency department (ED) received 42 doses of Vernakalant. At an average of 8.8 minutes (2-30), 83% of patients had their sinus rhythm back, and nine required a second injection. Symptoms lasted an average of 11.9 hours (2-36). Sneezing (15%) and brief alterations in taste (20%). There were no significant differences between the cardioversion/noncardioversion groups in age (57.6/56.2 years), mean duration of symptoms (12.54/9.54 h), and mean heart rate (141/140 bpm). After two hours of monitoring in the ED, two patients who did not respond to Vernakalant were electrically cardioverted, four patients were discharged for outpatient cardioversion (because of resource limitations), and one patient was hospitalised for additional diagnostic testing. Four (9.5%) patients experienced a recurrence of AF, and no patients experienced thrombotic or bleeding events throughout the six-month follow-up period. 41/42 (97.5%) patients were discharged from the ED on the same day(18).

13. This study determined the acute effects of Vernakalant (RSD1235) on human electrophysiological (EP) properties. The participant group comprised ten male patients and nine female patients. Vernakalant (RSD1235) prolonged adequate refractory periods at the 600 msec drive cycle length for the lower dose. At the higher amount, there were no significant changes in ventricular effective refractory period at either dose, at either 400 msec or 600 msec pacing cycle lengths. There were no significant increases in QT interval during Atrial or ventricular pacing with either amount of Vernakalant (RSD1235) at 400 or 600 msec paced cycle length. There was a prolongation in QRS duration during ventricular pacing at 400 msec CL in the higher dose group (P=0.0547 by the Wilcoxon signed-rank test. There were also no significant trends in QRS prolongation during Atrial pacing at the higher dose and ventricular pacing at 600 msec cycle length. His Purkinje conduction increased during the higher-dose infusion of Vernakalant (RSD1235 (P=0.016). Sinus node recovery time was significantly prolonged at the 400 msec cycle length at the higher dose level (P=0.047). There were no significant effects of either dose of Vernakalant (RSD1235) on systolic or diastolic blood pressure, respiratory rate, or oxygen saturation. Three patients had an altered, metallic taste in the mouth, and four had circumoral paresthesia at the higher dose. These symptoms disappeared promptly after drug discontinuation(19).

12.This study was to illuminate the influence of Vernakalant on hemodynamics. The study covered ten intensive care unit (ICU) patients developing post-operative atrial fibrillation (POAF) after elective cardiac surgery. All ten patients were awake and breathing spontaneously. The patients before 20 min and after 120 min of the first dose of Vernakalant; were clinically observed and monitored for heart rate, invasive blood pressure, pulse oximetry, and central venous pressure (CVP) in 1 min. From the end of surgery until the occurrence of POAF, the median time was 52.8 [45.9–77.4] hours. From the circumstance of POAF until the Vernakalant’s first application, the median time was 3.5 [1.2–10.1] hours. The patients were supported with catecholamine (epinephrine) during the observational phase. A stable hemodynamic state was noted, with a tendency to fall in heart rate (HR) throughout the 120 minutes after the administration of Vernakalant. In 70% (7) of patients, conversion to sustained SR was obtained within 8.0 min [6.0–9.0]. No SAEs were recorded during the observation span. Conclusively, the Vernakalant could not produce a significant adverse effect on the hemodynamics of the patients (ICU patients showing POAF after cardiac surgery), but it produced sustained SR conversion in 70% of patients after a median of 8.0 min (20).

13.The randomized controlled trial aimed to compare Vernakalant and ibutilide for the time to conversion and the mutation rate in recent-onset AF within 90 min. The test was conducted on 100 patients with recent-onset AF treated at the ED of a tertiary care hospital. The patients gained two short infusions of vernakalant (n=49; 3 mg/kg followed by 2 mg/kg if required) or ibutilide (n=51; 1 mg followed by 1 mg more if needed). Clinical and laboratory variables, adverse events, conversion rates, and time to conversion were recorded. The Vernakalant showed a significantly shorter conversion time from AF to SR than ibutilide, with a median time of 10 vs. 26 min (P< 0.01). Vernakalant showed significantly higher conversion success from AF to SR than ibutilide within 90 min (69 vs. 43%, log-rank P< 0.002). No SAEs were observed during the study (21).

***Interaction with other drugs***

Vernakalant's pharmacokinetic profile shows fast dispersion and a brief half-life, which reduces the likelihood of drug-drug interactions. Vernakalant established synergistic, antagonistic, additive effects with many following drugs, but no interaction was found with food. No pharmacodynamic interactions were found between Vernakalant and propranolol, verapamil, or the anticoagulant warfarin. Several authors have hypothesised drug-drug interaction resulting from protein displacement.

 **Table No 3:** Pharmacokinetic interaction of Vernakalant on the following drugs.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Metabolism of Vernakalant ↑ | Metabolism of Vernakalant ↓ | ↑es arrhythmogenic activity of Vernakalant | The risk or severity of QTc prolongation | The risk or severity of adverse effects |
| Abatacept | Selegiline, Rosiglitazon,Rantidine, Omeprazole, Mepyramine, celecoxib, Chloroquine, Cimetidine, Cyclosporine, Hydroxycholroquine, Imipramine | Verapamil, Propafenone, Norfloxacin, Losartan, Lidocaine, Acetyldigitoxin, Amlodipine, Bretylium,digitoxin, Ethosuximide, Hyoscyamine | Sulfamethoxazole, Valproic acid, Salbutamol, Oxytocin, Ondansetron, Ofloxacin, Nalidixic acid, Metronidazole, Acrivastine, Amantadine, Apomorphine, Azithromycin, Cetrizine, Chlorpheniramine, Ciprofloxacin, Clarithromycin, Cocaine, disulfiram, domperidone,Famotidine,Haloperidol, Levocetrizine | Amiodarone |

***Contraindication***

Acute coronary syndrome, severe aortic stenosis, severe heart failure, systolic blood pressure less than 100 mmHg, acute coronary syndrome during the past 30 days, and QT prolongation more significant than 440 msec are all contraindications to using Vernakalant. Vernakalant is also not advised if you recently received intravenous class I or class III antiarrhythmic medication. Not many individuals have severe liver disease, hypertrophic obstructive cardiomyopathy, restrictive cardiomyopathy, constrictive pericarditis, or clinically significant valvular stenosis. The left ventricular ejection fraction is rarely less than 35%.

***Adverse events and serious adverse events***

The safety profile of oral Vernakalant is similar to intravenous Vernakalant in the first 24 hours. In addition, there were no episodes of torsade de pointes in both formulation studies(8).

Table No 4: Commonly developed AE and SAE of Vernakalant.

|  |  |
| --- | --- |
| **Adverse event** | **Serious Adverse event** |
| Cardiac disorders | Ventricular fibrillation |
| Ventricular tachycardia | Arterial blood pressure of 49/39 mm Hg |
| Sinus arrest  | Complete AV block |
| Dysgeusia | Ventricular tachycardia  |
| Sneezing | Sustained zoomorphic |
| Paresthesia | Ventricular fibrillation  |
| Dizziness | Bradycardia  |
| Bradycardia | Sinus arrest  |
| Nausea  | Urinary retention  |
| Hyperhidrosis | Troponin T increase  |
| Hypotension | Atrial thrombosis  |
| Pruritus | Syncope (related to pulmonary embolism) |
| Cough  | Bradycardia of 40 beats per min lasting <5 min |
| Lacrimation increased  |  |
| Transiently altered taste  |  |

***Toxicology***

Rat shows the highest resistance among laboratory animals due to ion channel blockade. No observed adverse effect was established from the single and repeated dose study on Vernakalant. In addition, there was no effect on mating, oestrous cyclicity, sperm parameters, other fertility indices, pregnancy, or litter parameters.

**Conclusion**

Neurological effects such as ataxia, head shaking, splayed posturing, reduced proprioception, coarse tremor, and decreased locomotor activity were reported in atrial fibrillation screening on laboratory animals. Vernakalant hydrochloride is a marked atrial selective antiarrhythmic agent. According to clinical trials, the most effective formulation of Vernakalant is intravenous formulation. It is a potassium channel blocker (IKur) and sodium channel blocker, which defines it as responsible for antiarrhythmic potency. In the 24 hours from the start of drug infusion, Vernakalant prolonged QRS, QT, QTcB, and QTcF and induced hypotension and Bradycardia. Theexisting studies reveal its efficacy in its parenteral formulation in terminating recent-onset AF. Sex, age, hepatic, and kidney function do not intend to affect the pharmacokinetic properties of Vernakalant. The most severe adverse event was of cardiac origin with hospitalisation. During the first 24 hours, adverse events in patients were dysgeusia, sneezing, paresthesia, nausea, and hypotension. The oral formulation is being studied for long-term maintenance of sinus rhythm after its first attempt, is currently under development, and has shown significant yield. It also provides an effective therapeutic alternative for converting AF with an acceptable safety profile in patients with a history of ischemic heart disease (IHD).

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