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VERNAKALANT HYDROCHLORIDE FOR THE RAPID CONVERSION OF RECENT-ONSET ATRIAL FIBRILLANTION: PHARMACOLOGY, CLINICAL EFFICACY, AND SAFETY

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ABSTRACT

Background: Atrial fibrillation is a common arrhythmia associated with stroke risk. Vernakalant hydrochloride is an intravenous, atrial-selective antiarrhythmic developed for the rapid conversion of recent-onset AF, offering an alternative to amiodarone, which may cause systemic toxicities. **Objective:** To review the pharmacological properties, mechanism of action, pharmacokinetics, clinical efficacy, and safety profile of intravenous vernakalant in patients with recent-onset AF. **Methods:** Pharmacological studies and clinical trials evaluated vernakalant using a 3 mg/kg intravenous infusion over 10 minutes, followed by an optional 2 mg/kg dose after 15 minutes. The maximum doses were 339 mg and 226 mg, respectively. **Results:** Vernakalant blocks atrial sodium and potassium channels, slowing atrial conduction and prolonging refractoriness. A 3 mg/kg infusion followed by 2 mg/kg, if needed, rapidly converts recent-onset AF to sinus rhythm. Its half-life is approximately 3 hours in extensive CYP2D6 metabolizers and 5.5 hours in poor metabolizers. Common adverse effects include hypotension, nausea, dizziness, dysgeusia, bradycardia, and arrhythmias.

KEYWORDS: Pharmacological cardioversion, Atrial-selective antiarrhythmic; Sodium-channel blockade; Potassium-channel blockade; Intravenous therapy; Drug safety.

INTRODUCTION

Atrial fibrillation (AF) is the most frequently occurring cardiac arrhythmia worldwide, affecting millions of individuals. Its prevalence is expected to continue increasing due to the ageing population and the growing number of associated risk factors..[1] Patients with atrial fibrillation may experience symptoms such as shortness of breath and chest pain, and the condition can lead to severe complications, particularly stroke.[2] To minimize the risk of stroke in patients with atrial fibrillation, anticoagulant therapy is commonly prescribed along with heart rate–controlling medications, including β-adrenoceptor antagonists (β-blockers).[3]

Restoration and maintenance of sinus rhythm is also a major approach for the management of AF. However, established drugs for achieving this goal are limited by either modest efficacy and/ or side effects, such as life-threatening ventricular pro-arrhythmias or severe extra cardiac toxicities.[4] For example amiodarone, which is generally considered to be the most effective drug for the treatment of AF and has low pro-arrhythmic potential, is associated with serious systemic side effects.[5] In 2009, a derivative of amiodarone that was developed with the aim of overcoming these limitations, dronedarone (Multaq; Sanofi–Aventis), was approved for AF, although it might not be as effective as amiodarone in maintaining sinus rhythm.[6]

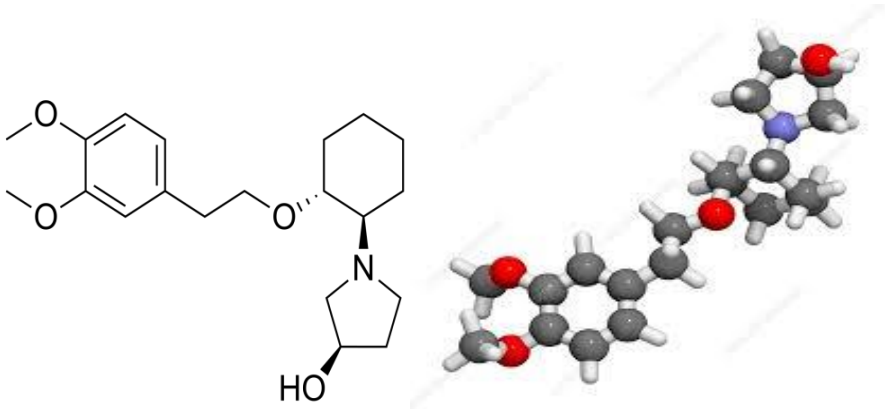

Fig 1: Molecular Structure of Vernakalant.

(3R)-1-{(1R,2R)-2-[2-(3,4-dimethoxy- phenyl) ethoxy] cyclohexyl} pyrrolidin-3-ol;

CHEMICAL FORMULA

C20 H31NO4

BRAND NAME

Brinavess

MANUFACTURE BY

Vernakalant was initially developed by Cardiome Pharma, and the intravenous formulation was bought for further development by Merck in April 2009.

INDICATION

Indicated for the rapid conversion of recent onset of Atrial fibrillation to sinus rhythm in adults for non-surgery patient that last for less than 7 days of duration and post cardiac surgery patient with atrial fibrillation lasting less than 3 days of duration.

ROUTE ADMINISTATION

Inter venous

DOSAGE

Total dose = 339 mg over 10 minutes · If no cardioversion after 15 min, give a further 226 mg infusion over 10 minutes.

Body weight: ≥40 kg and <113 kg

- Infusion **3 mg/kg** over 10 minutes.
- If no cardioversion after 15 min, give a further **2mg/kg** infusion over 10 minutes

Body weight ≥113kg

- Infusion: Total dose = **339 mg** over 10 minutes.
- If no cardioversion after 15 min, give a further **226 mg** infusion over 10 minutes.

ABSORPTION

In patient, average peak plasma concentration of vernakalant were 3.9 µg/ml following a single 10minute infusion of 3 mg/kg vernakalant hydrochloride, and 4.3 µg/ml following a second infusion of 2mg/kg with a 15minute interval between doses.

MECHANISM OF ACTION

Vernakalant dose- and rate-dependently blocks atrial voltage-gated sodium channels, decreasing late sodium current (INa) and slowing intra-atrial conduction. The drug's affinity for INa increases at higher heart rates, accelerating onset of blockade, while effects reverse quickly as rate falls. It also targets atrial-specific potassium currents Kv1.5 (IKur) and acetylcholine-activated channels (IKAch)—lengthening atrial refractoriness. Vernakalant inhibits Kv4.3-mediated Ito, which mainly affects atrial repolarization, and has minimal effect on hERG/IKr, accounting for only modest QT prolongation; QRS widening from INa block contributes additionally.[7] The Molecular Targets and Blocking Actions in Humans were displayed in Table 1.

Table 1: Molecular Targets and Blocking Actions in Humans.

TARGET	ACTION	ORGANISM
Sodium channel protein type 5 subunit alpha	Blocker	human
Potassium voltage-gated channel subfamily A member 5	Blocker	human
A-type voltage-gated potassium channel KCND3	Blocker	human
Voltage-gated inwardly rectifying potassium channel KCNH2	blocker	human

PHARMACOLOGICAL ACTION

PHARMACODYNAMICS.[8]

Vernakalant affects multiple phases of the atrial action potential by inhibiting atrial-selective potassium currents, including the ultra-rapid delayed rectifier and acetylcholine-activated potassium currents. It increases atrial refractory periods in a dose-related manner and prolongs AV nodal conduction and refractoriness. Although it may cause a slight widening of the QRS complex, it has minimal influence on ventricular refractory periods. Because its primary action is directed toward ion channels involved in atrial repolarization, vernakalant is considered to have a relatively low risk of inducing ventricular proarrhythmia.

PHARMACOKINETICS[10]
In individuals with reduced CYP2D6 activity, vernakalant is primarily metabolized through glucuronidation and subsequently eliminated by the kidneys. Its elimination half-life is approximately 3 hours in CYP2D6 extensive metabolizers and extends to about 5.5 hours in poor metabolizers.

VOLUME OF DISTRIBUTION[12]
Approximately 2L/kg.

ABSORPTION
Following intravenous administration, the mean peak plasma concentration of vernakalant was approximately 3.9 μg/mL after the initial 3 mg/kg infusion given over 10 minutes. When a second 2 mg/kg infusion was administered after a 15-minute interval, the concentration increased to approximately 4.3 μg/mL.

PROTEIN BINDING[12]
Displays low protein binding and the free fraction of vernakalant in human serum is 53-63% at concentration range of 1-5 μg/ml.

ROUTE OF ELIMINATION[10-12]
Mainly eliminated via renal excretion.

HALF-LIFE[10]
Elimination half-life in CYP2D6 extensive metabolizers is 3 hours and 5.5 hours in poor metabolizers.

TOXICITY[11]
Some common unwanted effects include hypotension, ventricular arrhythmias, bradycardia, atrial flutter, dysgeusia, paraesthesia, dizziness and nausea.

METABOLISM[10]
Vernakalant is metabolized in the liver by cytochrome P450 (CYP2D6). The main metabolism pathway depends on the CYP function of individual. CY P2D6 extensive metabolizers.

- The main route of degradation is O-demethylation by CYP2D6.
- The elimination half-life is about three hours.

MATERIALS AND METHODS
CLINICAL TRIAL
Electrophysiological investigations found that vernakalant predominantly prolongs atrial refractoriness, with considerably less effect on ventricular refractory periods. It also increases AV nodal refractoriness, extends the Wenckebach cycle length, and delays recovery of the sinus node. At rapid pacing rates, a modest widening of the ventricular QRS complex may occur; however, the drug does not appear to significantly alter paced or spontaneous atrial QRS or QT intervals.[8]

The CRAFT study evaluated different sequential dosing schedules of vernakalant, with each infusion administered over 10 minutes and separated by a 15-minute interval. The 2 mg/kg–3 mg/kg regimen produced better AF conversion than the lower-dose regimen, achieving termination in 11 of 18 patients (61%). Because many conversions occurred after the second infusion, the dosing sequence was subsequently reversed to 3 mg/kg followed by 2 mg/kg for later clinical trials.[9] The AVRO Trial Study Design and Patient Monitoring Schedule were displayed in Fig 2.

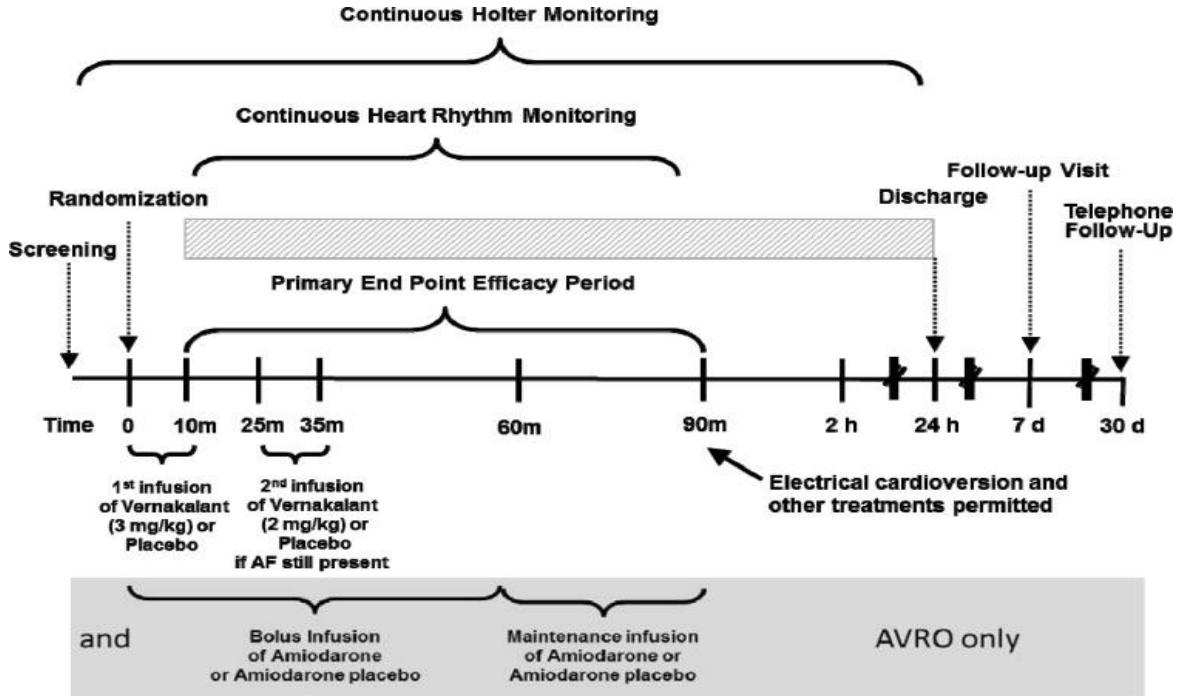

Fig 2: AVRO Trial Study Design and Patient Monitoring Schedule.

Schematic of the clinical trials for the development of vernakalant. All trial used sinus rhythm at 90 minutes after the start of the vernakalant infusion as the primary endpoint. In CRAFT the infusion doses were reversed.[13]

METHODS

STUYD DESIGN

This phase III study was a multicenter, randomized, double-blind, placebo-controlled trial designed to evaluate the efficacy and safety of vernakalant in patients with recent-onset AF across the Asia–Pacific region (ClinicalTrials.gov: NCT01174160). The protocol was approved by the relevant ethics committees or institutional review boards at all participating centers. The trial followed the Declaration of Helsinki and Good Clinical Practice standards, with oversight from the study sponsors and an independent clinical events committee. All participants provided written informed consent before enrolment.[14]

PATIENT SCREENING AND SELECTION

Participants were adults aged 18–85 years, weighing 45–136 kg, who had symptomatic, recent-onset AF lasting from 3 hours to 7 days. Before screening, patients were required to remain hemodynamically stable for at least 12 hours, maintain adequate hydration, and receive anticoagulation according to the investigator's assessment. The study population included patients with structural heart disease, with its prevalence restricted to approximately 20%–60%.[14]

TREATMENT PLAN

If after a 15-minute observation period, patients were in AF or atrial flutter, a second 10-minute infusion of vernakalant (2 mg/kg) or equivalent volume of placebo was administered, unless any dose-stopping criteria had been met. Patients Flow During the Treatment Phase were displayed in Fig 3.

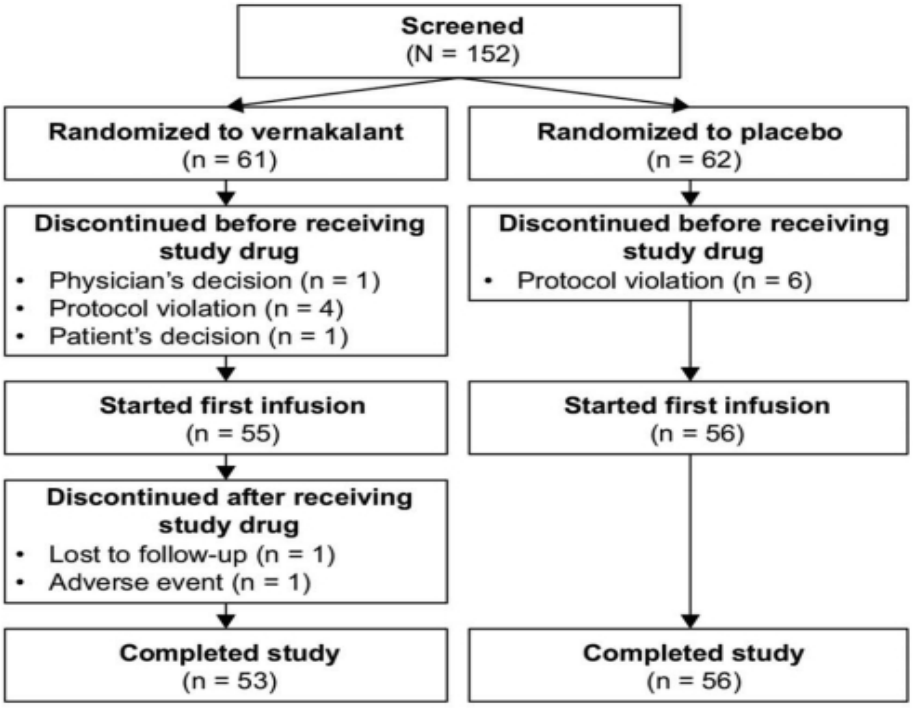

Fig 3: Patient Flow During the Treatment Phase.

CONDUCTION VELOCITY

During atrial fibrillation (AF), inhibition of sodium channels (INa) slows atrial conduction velocity (CV), whereas selective IKr blockade has little effect. Although slower conduction may help terminate re-entrant circuits by promoting conduction block, it can also facilitate re-entry. Sodium channel blockade also prolongs the temporal excitable gap, influencing AF termination. Before successful cardioversion, conduction velocity often increases with sodium or potassium channel blockers. However, in focal AF, changes in conduction velocity have minimal effect on ectopic activity. Overall, the precise role of conduction velocity in drug-induced AF cardioversion remains unclear.[15] The Mechanism of Atrial Wavelength (WL) Prolongation by Antiarrhythmic Drugs were displayed in Fig 5.

WAVELENGHT

During the 1980s and 1990s, atrial wavelength (WL) was widely regarded as an important predictor of the antiarrhythmic effectiveness of drugs used to treat atrial fibrillation (AF). This view was based on studies showing that sodium channel (INa) and rapid delayed rectifier potassium channel (IKr) blockers suppressed AF by increasing WL. The Mechanism of INa and IKr Blockers in Atrial Fibrillation Termination were displayed in Fig 4.

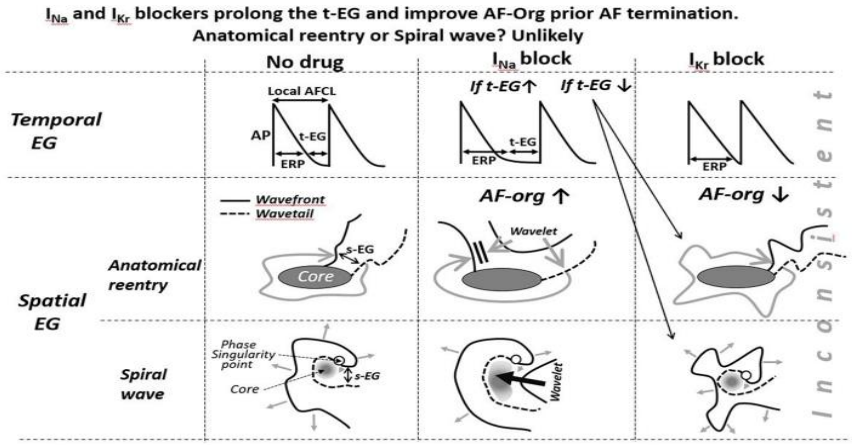

Fig 4: Mechanism of INa and IKr Blockers in Atrial Fibrillation Termination.

However, more recent evidence indicates that AF can be successfully terminated even when WL is shortened, prolonged, or remains unchanged, suggesting that WL alone is not a dependable indicator of drug-induced cardioversion. Furthermore, any increase in WL produced by antiarrhythmic drugs primarily results from prolongation of the effective refractory period (ERP), since slowing of conduction velocity (CV) tends to reduce WL. Therefore, ERP prolongation, rather than changes in WL itself, is likely the principal mechanism responsible for the antiarrhythmic effects of these drugs.[15] The Mechanism of Atrial Wavelength (WL) Prolongation by Antiarrhythmic Drugs were displayed in Fig 5.

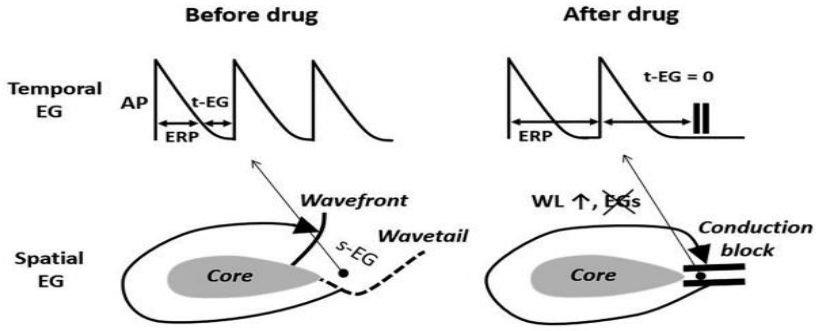

Fig 5: Mechanism of Atrial Wavelength (WL) Prolongation by Antiarrhythmic Drugs.

SIDE EFFECT

Vernakalant Hydrochloride is an effective treatment for atrial fibrillation, it is associated with several potential side effects. Common side effects include taste disturbances, nausea, and hypotension, while more serious side effects can include bradycardia, respiratory issues, allergic reactions, arrhythmias, and liver function abnormalities.[16] The Common and Uncommon Adverse Reactions to Vernakalant were displayed in Table 2.

Table 2: Common and Uncommon Adverse Reactions to Vernakalant.

VERY COMMON	COMMON	UNCOMMON
Dysgeusia Sneezing	Dizziness Headache Paraesthesia Bradycardia Hypotension Cough Nausea and vomiting Pruritus	Vasovagal syncope Eye irritation Visual impairment Sinus arrest Complete heart block LBBB/RBBB Ventricular tachycardia Ventricular ectopics Prolonged QT Flushing Dyspnoea Diarrhoea Infusion site irritation

LICENCE[17]

- The EU approved vernakalant in 2010 for the cardioversion of AF of less than 7 days in duration, or for post-operative AF le18-03-2025ss than 3 days in duration.
- Vernakalant has been marketed in some, but not all European countries. Other countries, notably in Asia, have also approved the drug.
- It's not approved in the USA.

CONCLUSION

Vernakalant is an atrial-selective antiarrhythmic agent that provides rapid and effective pharmacological cardioversion of recent-onset atrial fibrillation (AF). By selectively blocking atrial sodium and potassium ion channels, it prolongs the effective refractory period with minimal effects on ventricular repolarization, thereby reducing the risk of ventricular proarrhythmia. Clinical trials have demonstrated its high efficacy, rapid onset of action, and favorable safety profile in appropriately selected patients. Although transient adverse effects such as dysgeusia, sneezing, nausea, and hypotension are relatively common, serious adverse events are uncommon when the drug is administered according to recommended guidelines. Vernakalant has been approved in Europe and several other countries for the treatment of recent-onset AF, but it has not received approval in the United States. Overall, vernakalant represents a valuable therapeutic option for the rapid restoration of sinus rhythm in patients with recent-onset atrial fibrillation.

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