Vernakalant hydrochloride in the treatment of atrial fibrillation: a review of the latest clinical evidence

Clin. Invest. (2011) 1(4), 579-588

Pharmacological cardioversion is still a fundamental and readily available instrument to control symptoms and promptly restore sinus rhythm in atrial fibrillation. A rapidly acting, efficacious and safe agent that targets the fibrillating atria without affecting ventricular refractoriness is highly desirable. Among newer atrial-selective antiarrhythmic agents, vernakalant is in the most advanced phase of investigation and its intravenous formulation has recently been approved in the EU for atrial fibrillation pharmacological cardioversion. The present article reviews vernakalant's pharmacological features and safety and efficacy as emerged from clinical trials performed so far to give a comprehensive vision of available data and to discuss implications for the clinical practice in atrial fibrillation management.

Keywords: antiarrhythmic drug • atrial fibrillation • atrial repolarization-delaying agents • atrial-selective compounds • pharmacological cardioversion • rhythm control • RSD1235 • vernakalant

Atrial fibrillation (AF) is the most common sustained arrhythmia [1] in clinical practice and its prevalence is expected to rise exponentially as the population ages, with the number of patients affected estimated to double in the next 50 years [2].

The main aims in AF management are to prevent complications and to reduce disabling symptoms. The only proven strategy to prevent AF-related complications and to improve survival is antithrombotic therapy.

Efforts aimed to restore and maintain sinus rhythm (SR) failed to show any differences in long-term survival compared with rate-control strategy in several randomized controlled trials [3,4]. Nevertheless, antiarrhythmic drugs (AADs) are a fundamental instrument in the management of AF, especially if a rhythm-control strategy is necessary to control symptoms or a prompt SR restoration is needed in acute settings.

Although electric cardioversion (CV) is more effective than drug administration, it requires general anesthesia from which patients must recover and the procedure may incur a significant time delay if the patient has recently eaten. There are also the inherent risks of sedation or anesthesia as well as the associated costs. Electrical CV may be associated with adverse effects (AEs) such as heart block, prolonged sinus arrest, dermal injury and pacemaker or internal defibrillator malfunction [5].

Pharmacological CV is easier to perform as drugs are readily available, it does not require general anesthesia and may facilitate the choice of AAD therapy to prevent recurrences.

Unfortunately, currently available antiarrhythmic agents used to perform pharmacological CV have a modest efficacy, a delayed onset of action, slow metabolism or undesirable side effects, including ventricular proarrhythmias [6]. Serious proarrhythmias are mainly caused by the actions of drugs on ventricular action potential duration that may be associated with QT-interval prolongation and risk of Torsades de Pointes (TdP) or on atrioventricular conduction and risk of 1:1 atrial flutter (AFI).

Alessandro Marinelli¹¹, Iacopo Ciccarelli¹ & Alessandro Capucci^{1,2}

¹Università Politecnica delle Marche, Azienda Ospedaliero Universitaria Ospedali Riuniti, Clinica di Cardiologia, Via Conca 71, Località Torrette, 60126 (AN), Italy ²Director of Clinica di Cardiologia, Ospedali Riuniti di Ancona, Italy ^{*}Author for correspondence: Tel.: +39 071 596 5034 Fax: +39 071 596 5624 E-mail: marinelli.doc@gmail.com



Several antiarrhythmics exploiting new mechanisms of action are currently under active investigation [7]. Among them we find agents that selectively inhibit ion channels specifically involved in atrial repolarization, so-called 'atrial repolarization-delaying agents' or 'atrial-selective compounds'. They are widely acknowledged as potentially ideal antiarrhythmic treatments [8], as they will probably be both effective and safe because of their atrial selectivity, a desirable feature to avoid ventricular proarrhythmia.

A rapidly acting, efficacious and safe drug that targets the fibrillating atria without affecting ventricular refractoriness is highly desirable and would be a valuable alternative to current AF treatments. In addition, prompt pharmacological conversion and reduction in hospitalization duration may prove to be a cost-saving strategy.

Vernakalant

Among several potential atrial selective AADs in clinical development, vernakalant (3-pyrrolidinol, 1-[(1R, 2R)-2-(2-[3,4-dimethoxyphenyl]ethoxy) cyclohexyl]-B hydrochloride [3R]-; RSD1235, Cardiome/Astellas) is in the most advanced phase. It is a new AAD that has been demonstrated to act selectively on the atrium by only delaying atrial repolarization. It does this by selectively acting on K⁺ channels primarily expressed in the atrium, thus resulting in atrial-specific prolongation of the effective refractory period. This makes vernakalant extremely valuable in treating atrial arrhythmias since it appears not to cause ventricular arrhythmias. Intravenous vernakalant was recently granted marketing approval (BrinavessTM) in the EU for the rapid conversion of recent-onset AF lasting less than 7 days in nonsurgery patients and less than 3 days in postoperative AF. In 2007, the US FDA Cardiovascular and Renal Advisory Committee recommended the approval of intravenous vernakalant [101], but the drug is not yet available for clinical use in the USA until more safety and efficacy data are accumulated. Vernakalant is also being evaluated in oral form for maintaining SR in patients with recurrent AF. The present article reviews pharmacological features, AEs, safety and clinical evidences available from clinical trials performed so far on vernakalant use in the management of AF.

Mechanism of action

Vernakalant is a mixed blocker of both K⁺ and Na⁺ channels that acts selectively on atrial tissue [9]. Its atrialselective action is explained both in targeting channels mainly found in atrial tissue (and not in the ventricles) and in its rate- and voltage-dependent efficacy, which leads to a greater reduction in impulse conduction velocity and tissue excitability when the heart rate is high, such as in AF.

Among channels conferring atrial selectivity to vernakalant we find the Kv1.5 channel, which carries the ultra-rapidly activating delayed rectifier potassium current (IK_) [10], and the Kir3.1/3.4 channel, which carries the acetylcholine-dependent potassium current (IK_{Acb}) . IK_{ur} is an atrial-specific current which contributes to atrial but not ventricular repolarization, and its block may confer an atrial-selective prolonging effect on action potential duration [11]. IK_{Ach} current is activated by vagally released acetylcholine and contributes to the shortening of action potential duration. It is involved in induction and perpetuation of AF and it was shown to develop a constitutive activity (no longer requiring its natural agonist acetylcholine) in chronic AF forms [12]. Blocking IK_{Ach} current vernakalant may, therefore, contribute to reduce the increased atrial vulnerability and to alter, in some way, the electrical remodeling process occurring during AF. Vernakalant can also block the transient-outward (I_n) and rapidly activating delayed rectifier (IK) potassium currents.

Vernakalant does not inhibit the slow component of delayed rectifier potassium current (IK_s) nor the inward rectifier current (I_{K1}), both important in ventricular repolarization. Although vernakalant showed action on the I_{Kr} involved in ventricular repolarization, its potency is 30- to 100-fold less than that of other AADs such as quinidine or propafenone [9], thus the proarrhythmic risk due to QT prolongation is minimized.

Vernakalant also shows relevant effects on Na⁺ channels. It blocks inward sodium current, such as the peak transient current, responsible for rapid upstroke of action potential. Sodium currents blockade, is less potent than IK, blockade but its potency increases in a voltage- and frequency-dependent manner. Therefore, the blocking action is greater at the high rates and in the depolarized atrial cells during AF, leading to a reduction in conduction velocity and tissue excitability and conferring a 'pathology'-selective action [9,13]. It also blocks the persistent current, a very slowly inactivating component of inward sodium current that is not directly involved in AF mechanisms but may counter the action potential prolongation in the ventricle. Blocking this late component, vernakalant may prevent or reduce early after depolarizations, the mechanism underlying long-QT syndrome arrhythmias, such as TdP [14]. In addition, there is increasing recognition of the importance of sodium channels in AF pathogenesis [15] and vernakalant's late sodium inhibition properties may, therefore, contribute to its efficacy.

In conclusion, vernakalant is able to inhibit many ion currents involved in myocardial repolarization and depolarization. The potential mechanisms to explain its efficacy are several and some still remains to be understood. However, among its favorable features it has a much greater effect in atrial tissue than in the ventricle, especially during high rates (e.g., during AF), and it is less likely to be proarrhythmic.

Pharmacokinetic properties

The pharmacokinetic profile of intravenous vernakalant has been explored in normal volunteers as well as in patients with AF or AFl [16]. Vernakalant demonstrated first-order elimination and linear pharmacokinetic properties in the dose range of 0.1-5 mg/kg following a 10 min intravenous infusion [102]. Its rapid and extensive distribution leads to a decrease in serum concentration by >40% within 5 min after the end of infusion. Vernakalant is not extensively bound to plasma proteins and is cleared both by the liver and the kidney. Hepatic metabolism is performed mainly by the CYP2D6 enzyme and it is the prevalent mechanism among the majority of individuals (extensive metabolizers [EMs]). Renal excretion is otherwise the main mechanism of clearance in poor metabolizers (PMs). In any case, dose adjustment based on metabolizer status is not necessary, thanks to the wide distribution volume of the compound. The mean elimination half-life is 3-5.5 h, in EMs and PMs respectively.

Studies did not show age, race, sex, renal function and heart failure (HF) as having any significant effect on pharmacokinetic properties of vernakalant [16]. In patients with hepatic impairment, exposures were elevated by 9–25%. Available pharmacokinetic parameters derive from patients receiving up to two doses for acute termination of AF, but no data are available on longterm oral therapy. Drug interaction studies involving vernakalant are limited; however, specific studies showed that β -blockers and CYP2D6 inhibitors did not affect its pharmacokinetic properties [17]. The oral bioavailability of vernakalant is approximately 20%. During oral therapy in the dose range of 300-600 mg twice daily, steady-state concentrations are achieved within 4 days. It remains to be seen whether CYP2D6 poor and extensive metabolizers will require different doses during chronic oral therapy [18].

Clinical efficacy

Both intravenous and oral forms of vernakalant have undergone clinical trials, the first for rapid SR conversion of recent onset AF, the latter in long-term SR maintenance.

The antiarrhythmic efficacy of intravenous vernakalant has been evaluated in one Phase II study, three Phase III randomized, double-blind, placebo-controlled trials, one uncontrolled and one active-control randomized study (Table 1).

The Conversion of Recent Onset Atrial Fibrillation Trial (CRAFT) was a Phase II dose-ranging study performed to establish efficacy and safety of intravenous vernakalant in patients with AF [19]. In this study, 56 patients with recent-onset AF (3–72 h duration) were randomized to one of two vernakalant dose groups or to placebo. The vernakalant groups received either 0.5 or 2 mg/kg initial infusion of the agent over 10 min, followed by either 1 or 3 mg/kg second infusion if normal SR was not restored within 15 min. Patients treated with the higher dose of vernakalant had a greater rate of AF termination compared with placebo (61 vs 5%; p < 0.0005). The median time to conversion was 14 min and no serious AEs were reported.

This trial led to four Phase III studies [20–23], the Atrial Arrhythmia Conversion Trials (ACT) 1-4 (Figure 1). ACT 1 and ACT 3 were similar in design. Patients were randomly assigned to receive vernakalant or placebo, and a 3-mg/kg infusion was infused first, followed by a second infusion of 2 mg/kg 15 min later if AF was not terminated. Pooled analyses demonstrated that the conversion rates for vernakalant and placebo were 51.1 and 3.8% (p < 0.0001). Only patients with short-duration AF (defined as lasting from 3 h to 7 days) showed significant changes in the rate of conversion, with a median time to efficacy in ACT 1 and ACT 3 of 11 and 8 min, respectively. The conversion was durable at 24 h and almost all patients successfully converted. Vernakalant was ineffective for the conversion of AF lasting more than 7 days and for AFl.

ACT 2 was designed to evaluate efficacy and safety of the compound in SR conversion of patients with postoperative AF or AFl. In 150 patients with AF after coronary artery bypass grafting or valve surgery, vernakalant showed similar efficacy as in ACT 1 and 3 trials, and superiority to placebo (47% conversions within the first 90 min of dosing compared with 14% in placebo group; p < 0.001). None of the ten patients with AFl converted to normal rhythm, confirming that the drug is not effective for this arrhythmia.

ACT 4 was a multicenter, open-label study designed to further assess the safety of intravenous vernakalant. A total of 167 patients with AF lasting from 3 h to 7 days were enrolled, and the 50.9% rapidly converted to SR with vernakalant infusion. Although not a prespecified efficacy population, patients with shorter duration AF (lasting \leq 48 h) had even greater success rates (57.9% of conversion) with vernakalant. Another important finding was the low incidence of early recurrence of AF, defined as recurrence that often occurs within minutes of electrical CV. Of the vernakalant-treated patients who converted within 90 min, 98.8% were in SR at 8 h; and 97.4% at 24 h.

An additional randomized, placebo-controlled trial specifically requested by the FDA in 2008 before approval of the drug is currently being conducted to further

Table 1	. Clinical trials on	າ efficacy and s	safety of v	vernakalant in atrial fib	vrillation.			
Trial	Inclusion criteria	Exclusion criteria	Patients (n)	Dose of vernakalant	Primary end point	Secondary end point	Comments	Ref.
CRAFT	AF 3–72 h	Reversible causes of AF, CHF	56	iv. 2 mg/kg, followed by 3 mg/kg if no conversion or iv. 0.5 mg, followed by 1.0 mg/kg if no conversion	Conversion to SR within 30 min: 61% (V) vs 5% (P) (p < 0.001)	SR at 1 h: 53% (V) vs 5% (P) (p = 0.0014) SR at 24 h: 79% (V) vs 45% (P) (p = 0.005)	Only the higher dose was effective Median time to conversion: 14 min	[14]
ACT 1	AF 3 h–45 days	NYHA IV	336	iv. 3 mg/kg. followed by 2 mg/kg if no conversion	Conversion to SR within 90 min in AF 3 h-7 days: 51.7% (V) vs 4% (P) (p < 0.001)	Median time to conversion 11 min SR at 24 h: 98% (V) Conversion of long duration AF (8–45 days): 7.9% (V) vs 0% (P): NS	Highest conversion rates for AF: ≤72 h (78%) NS conversion of AFI	[15]
ACT 2	AF or AFI (3–72 h) after CABG or valvular surgery	Reversible causes of AF, NYHA IV	150	iv. 3 mg/kg, followed by 2 mg/kg if no conversion	Conversion of AF/AFI to SR within 90 min: 44.9% (V) vs 14.8% (P) (p < 0.001)	AF Converted to SR: 47% (V) vs 14% (P) ($p < 0.001$) Median time to conversion: 12 min No conversion of AFI to SR	NS differences between CABG vs valvular surgery patients	[16]
ACT 3	AF or AFI 3 h–45 days	NYHA IV	265	iv. 3 mg/kg, followed by 2 mg/kg if no conversion	Conversion to SR within 90 min in AF 3 h–7 days: 51.2% (V) vs 3.6% (P) (p < 0.0001) NS conversion of AF 8–45 days	Median time to conversion: 8 min NS conversion of AFI to SR	Highest conversion rates for AF: ≤72 h (71%) No 1:1 conduction in AFI subgroup	[17]
ACT 4	AF 3 h–45 days	Reversible causes of AF, NYHA IV	236	iv. 3 mg/kg, followed by 2 mg/kg if no conversion	Conversion to SR within 90 min in AF 3 h–7 days: 50.9%	Low rates of ventricular arrhythmias (6%) No TdP reported	Median time to conversion: 14 min	[18]
AVRO	AF 3–48 h	NYHA IV	232	iv. 3 mg/kg, followed by 2 mg/kg if no conversion vs iv. amiodarone (bolus 5 mg/kg + 50 mg 2 h infusion)	Conversion to SR within 90 min: 51.7% (V) vs 5.2% (A) (p < 0.0001)	Median time to conversion: 11 min (V) vs 25 min (A) Symptom free at 90 min: 53% (V) vs 33% (A)	Lower rate of hypotension due to more attention to hydration status	[19]
ACT: Atri <i>a</i> CABG: Co	al Arrhythmia Conversio sronary artery bypass gr	n Trial; A: Amiodaro aft; CHF: Congestiv	one; AF: Atrial e heart failur€	fibrillation; AFI: Atrial flutter; AV e; iv.: Intravenous; NS: Nonsigni	/RO: Active-Controlled Superiority ⁽ ficant; NYHA: New York Heart Asso	study of Vernakalant Versus Amiodarone ciation; P: Placebo; SR: Sinus rhythm; TdP	e in Recent-Onset Atrial Fibrillation; P: Torsades de Pointes; V: Vernakalan	i.t

Review: Clinical Trial Outcomes Marinelli, Ciccarelli & Capucci

address the safety and efficacy of the compound (ACT 5; trial no. NCT00989001) [103]. At the time of writing, the study is on hold to evaluate a recent case of cardiogenic shock that occurred after drug infusion.

Vernakalant may also be useful for the prevention of AF recurrences. Phase III trials have not been completed for oral vernakalant, although results of Phase II trials have been promising in long-term SR maintenance [104].

The Phase IIa trial was a double-blind, placebo-controlled, randomized, doseranging study designed to explore safety and tolerability, pharmacokinetics and preliminary efficacy of oral vernakalant over 28 days of dosing in



Figure 1. Vernakalant for conversion of atrial fibrillation to normal sinus rhythm. AF: Atrial fibrillation; SR: Sinus rhythm.

patients at risk of recurrent AF. The majority of patients enrolled had AF lasting from more than 30 days and less than 180 days. A 300 mg and 600 mg twice-daily dosage of oral vernakalant and placebo were compared for 25 days after successful CV. Electrical CV was permitted for patients who did not convert within 3 days after initiation of the medication. Significantly more patients remained in SR at the end of the trial period in the 300 mg twice-daily dosing group (61%) and in the combined 300 and 600 mg twice-daily dosing groups (52%), when compared with placebo.

The Phase IIb trial compared 150, 300 and 500 mg twice-daily dosages with placebo, and the follow-up duration was 90 days. The 500 mg twice-daily dosage group showed durable maintenance of SR at 90 days compared with placebo (51 vs 37%; p = 0.0221), with low incidence of side effects and no reported cases of TdP.

The only direct comparative study regarding the AF conversion efficacy of vernakalant is the recent Active-Controlled Superiority Study of Vernakalant Versus Amiodarone in Recent Onset Atrial Fibrillation (AVRO) trial [24]. This randomized, double-blind study compared efficacy and safety of intravenous vernakalant (3 mg/kg 10-min infusion, followed by another 2 mg/kg 10-min if AF still present after a 15 min observation period) and amiodarone (5 mg/kg 60-min infusion, followed by an additional 50 mg over 60 min maintenance infusion) in acute conversion of recent-onset AF (<48 h duration). The primary end point was the proportion of patients achieving SR within 90 min. In 254 adult patients enrolled, vernakalant was demonstrated

to be superior to intravenous amiodarone, with 51.7% of patients in SR at 90 min in the vernakalant arm, compared with 5.2% of those in the amiodarone arm (p < 0.0001). In addition, vernakalant was associated with a higher rate of symptom relief. Serious AEs or events leading to drug discontinuation were uncommon. Although amiodarone may not be the ideal drug to be compared with vernakalant, especially if an observation period of only 90 min is chosen to assess the primary end point, at the moment no other comparative studies are available. Thus, comparisons of vernakalant with class IC agents and ibutilide are awaited with great interest.

Safety & tolerability

Considering its atrial selective properties, vernakalant is expected to be associated with a good safety profile and with a low proarrhythmic risk for inducing ventricular tachyarrhythmias.

In vivo human electrophysiology studies performed during vernakalant infusion showed slightly prolonged atrioventricular conduction time and sinus node recovery time, with no significant prolongation of the QT interval [13]. However, a significant increase in QRS and QT intervals as compared with placebo was documented in clinical trials. In the ACT I study, vernakalant prolonged QRS intervals from 100.1 \pm 16.6 msec (mean \pm SD) at baseline to a peak of 106 \pm 21.45 msec at the end of the 3 mg/kg-first infusion, whereas QRS intervals remained unchanged in placebo patients [20]. Prolongation of QTc was observed with placebo-subtracted peaks of +22.1 msec at 10 min and +18.8 msec

Review: Clinical Trial Outcomes Marinelli, Ciccarelli & Capucci



Figure 2. Mean time-to-conversion of intravenous antiarrhythmics used to restore sinus rhythm in atrial fibrillation.

at 35 min, returning to baseline by 50 min [105]. In any case, QT and QRS prolongation was only modest and not associated with proarrhythmia.

Vernakalant has a very short half-life, and AEs from intravenous formulation were considered to be drugrelated if they occurred within the first 24 h after drug infusion. After this period, most of the drug is supposed to be eliminated from the body.

Considering Phase II and III clinical trials together, the incidence of serious AEs during the 24 h postdose was slightly higher in the vernakalant group (2.1%) than in the placebo group (0.3%). Hypotension [105] was the most frequently vernakalant-related serious AE (1.0%). Other less-frequent serious AEs included sinus bradycardia (0.4%) and complete atrioventricular block (0.3%). A higher incidence of AFl occurrence is expected in patients treated with vernakalant but no cases of 1:1 atrioventricular conduction have been reported to date in clinical trials [105]. Patients with NYHA IV HF were excluded from all of these trials and only a few had either moderate or severe reduction of left ventricular ejection fraction.

Six cases of deaths were reported in the overall trial population, of which only one was considered related to vernakalant. This concerns a patient with severe aortic stenosis, acute coronary syndromes and hemodynamic instability at the time of drug administration, the recruitment of which represented a protocol violation. After two vernakalant infusions, the patient developed ventricular fibrillation followed by electromechanical dissociation and resuscitation efforts were unsuccessful.

With regard to clinically meaningful ventricular arrhythmias, they occurred with a slightly higher frequency in the vernakalant compared with the placebo

group. Among the five cases of ventricular arrhythmias occurring within the first 2 h after drug administration reported so far, three cases regarded patients with a history of HF. Two cases of ventricular fibrillation are reported, one in the patient with aortic stenosis who died (see previous paragraph) [22]; the other was attributed to asynchronous discharge during an electrical CV attempt performed 1 h following vernakalant infusion and, therefore, was considered unrelated to the drug [19]. There were actually three patients out of all pooled participants who developed TdP in the vernakalant group, of which only one might have a temporal

relation to the drug. This case was an asymptomatic 9-beat run of a ventricular arrhythmia occurring 2 h and 20 min after the initiation of the infusion of vernakalant injection and immediately after an infusion of ibutilide, which might have confounded the causal relation between vernakalant and TdP. In another two patients, TdP occurred 32 h and 16 days after treatment with vernakalant [20]. Generally, ventricular arrhythmia events occurred more frequently in patients with a history of HF who were treated with vernakalant, and in any case the low incidence rates were probably related to the exclusion of participants with recent myocardial infarction, reduced left ventricular ejection fraction and unstable NYHA IV HF. In any case, additional data are needed to drive any conclusion about this safety issue.

The overall incidence of hypotension in the first 2 h following drug infusion was comparable between the vernakalant and the placebo groups (7.6 vs 5.1%, respectively); however, the entity of hypotension (systolic blood pressure postdose <80 mmHg) was higher with vernakalant (2.9%) than with placebo (1.5%) [105]. The incidence of hypotension-associated AEs was higher among vernakalant-treated patients (5.4%) than among placebo-treated patients (1%). A history of HF or low baseline systolic blood pressure (<105 mmHg) were the most important factors that correlated to approximately a threefold increased risk of hypotension, indicating a possible negative inotropic deleterious effect of vernakalant in hemodynamically unstable patients (including patients with severe valvular heart disease). A much lower incidence of hypotension was reported in the AVRO trial [24] compared with previous studies, mostly due to exclusion of patients with systolic blood pressure ≤100 mmHg and to an adequate hydration and hemodynamic optimization before treatment.

The most common side effects associated with vernakalant infusion occurring within the first 2 h after dosing were dysgeusia (20.1%), sneezing (14.6%), paresthesias (7.8%), hypotension (4.0%) and nausea (4.5%) [105]. The majority of these effects were generally of mild or moderate in intensity, transient in duration and not treatment-limiting [25]. The rate of withdrawal was low and slightly higher in the vernakalant group (1.3%) compared with placebo group (0.9%).

In summary, the main safety issues associated with vernakalant infusion involve the cardiovascular system and include hypotension, cardiogenic shock, atrioventricular block and bradycardia. Cases of ventricular arrhythmia were infrequently reported, but that may also reflect the limited database.

At the moment of the writing of this article, enrollment in another additional Phase III vernakalant trial, the ACT 5 study [103] has been suspended following a single serious case of cardiogenic shock in a patient who received the drug [106]. Full data regarding this case are now being reviewed to clarify the mechanism underlying the event prior to restarting the study.

In any case, to improve the safety profile of the compound it should not be administered within 4 h following use of intravenous class I/III AADs nor in patients with severe hypotension, NYHA IV HF, acute coronary syndromes, bradycardia and prolonged QT at baseline.

The safety profile of the oral form is similar to that of intravenous vernakalant. No episodes of TdP were noted in the oral treatment studies and there were similar incidences of serious AEs in both placebo and vernakalant groups.

Conclusion & future perspective

Compared with other intravenous AADs used to restore SR in AF, vernakalant has been shown to have a very prompt (Figure 2 [19-24,26-33]) and safe effect, particularly in patients with recent-onset AF and good left ventricular function, even if with organic heart disease. It has been compared with amiodarone and demonstrated, as expected, a much higher efficacy in a short period of time.

Vernakalant's efficacy has not been compared, so far, to the very effective class IC AADs. It is likely that conduction velocity is the most important parameter to act on with drugs used for AF conversion. Therefore, it is the vernakalant conduction-delaying property that favors SR conversion. In this respect, it is unlikely to expect a much higher efficacy rate of conversions in absolute terms compared with IC AADs that also have Na⁺ channel-blocking properties. The most important result with vernakalant could be, therefore, to obtain a very fast reversion to SR in people with symptomatic AF. This result can be reached with vernakalant in a Table 2. Variation in sinus rhythm restoration rate of antiarrhythmic drugs and placebo in recent-onset atrial fibrillation according to different time-to-efficacy evaluation¹.

Drug	Efficacy (%)		Ref.	
	8 h	24 h		
Amiodarone	50-62	69–92	[26-28,30,35,36]	
Flecainide	67–92	67–92	[31,37,38]	
Propafenone	59–70	78–80	[26,29,30,39]	
Ibutilide	40–56	40-56	[32,33,40-42]	
Vernakalant	52–61	52–79	[19-24]	
Placebo	26–59	55-64	[26-41]	
⁺ The value of the table	is limited by the wide	considered time-to-eff	icacy evaluation in the	

different trials.

few minutes compared with 2–3 h with IC AADs. The use of the drug in first aid departments should thus be of 'special value'. In this respect, it is of major importance to evaluate whether the patient could be safely discharged earlier after SR restoration. The formula 'inject, convert and discharge' could be an innovative approach and really favorable in terms of cost efficacy.

The high rate of spontaneous conversion in recentonset AF (up to 50–64% within the first 24 h after onset) might raise concerns about usefulness of a new AAD for AF conversion [34]. Table 2 [19–24,26–33,35–42] shows the important variations in efficacy that can be observed for AADs and placebo according to different observation periods. However, waiting for spontaneous SR restoration is generally not applicable in clinical practice, unless the patient is both anticoagulated and asymptomatic. In addition, the success of CV is time dependent, especially for drug conversion, and the risk of thromboembolism also increases with time from AF onset, making a prompt SR resumption desirable.

Concerning safety, vernakalant proarrhythmic effects are not of major relevance and are limited to the acute infusion phase. Hypotension has been avoided by infusing the drug in a rightly hydrated patient and strictly monitoring blood pressure during the infusion phase

Table 3. Occurrence of Torsades de Pointes, hypotension and rapid conduction atrial flutter with antiarrhythmic drugs in cardioversion of recent-onset atrial fibrillation.

Drug	Torsade de Pointes (%)	Hypotension (%)	1:1 atrial flutter (%)	Ref.
Amiodarone	0.7	1.6-3.0	-	[26-28]
Flecainide/ propafenone	0.5	2.0	3.5–5	[26,27,31,37,43]
Ibutilide	3.6-5.6	2.0	-	[32,33,40-42,44]
Vernakalant	0.1	2.8-5.6	-	[19-24]

in most recent studies. As a general rule, AAD infusion should be avoided not only in people with a low ventricular rate but also in patients with AF and a particularly high ventricular rate when there is a systolic blood pressure decrease and contemporary diastolic enhancement, expression of an initial low cardiac output state. In this situation, an electrical CV is the preferable choice. Table 3 [19-24,26-28,31-33,37,40-44] shows the rate of occurrence of TdP, hypotension and rapid conduction of AFI occurring with the most commonly used AADs in AF cardioversion.

Vernakalant, therefore, seems to be safe and effective in selected AF populations in the short period after SR conversion and in the reduction of early recurrences. Further studies will also clarify the possible employment of the oral drug also for rhythm control. Vernakalant is, thus far, a very promising drug as a first treatment for AF, especially in first aid emergency departments. Future analyses should evaluate if a prompt SR restoration with a consequent reduction of in-hospital stay is a safe and cost-effective strategy in AF management.

Financial & competing interests disclosure

Alessandro Capucci was a temporary consultant for MEDA, Merck and Sanofi synthelabo. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Executive summary

- Pharmacological cardioversion is still a fundamental and readily available instrument to control symptoms and promptly restore sinus rhythm in atrial fibrillation and is often the first medical approach to this arrhythmia.
- Vernakalant hydrochloride is a rapidly acting and safe agent specifically targeting the fibrillating atria and its efficacy has been shown in different clinical trials.
- Intravenous vernakalant is currently approved in the EU for rapid pharmacological cardioversion of recent-onset AF.
- It has favorable pharmacodynamic and pharmacokinetic properties, with a very short time to efficacy and a short elimination half-life.
- The most common side effects occurring within the first 24 h after its use are dysgeusia, sneezing, paresthesias, nausea and hypotension.
- Vernakalant is associated with a good safety profile, with a low proarrhythmic risk for ventricular tachyarrhythmia consequently to its atrial selective properties.
- In any case, vernakalant should not be administered in patients with NYHA IV heart failure, severe hypotension, acute coronary syndromes within 30 days, severe aortic stenosis, bradycardia and prolonged QT or after use of class I/III agents because its safety in these settings has not been adequately explored.
- Comparative trials with other intravenous antiarrhythmic agents used for pharmacological cardioversion, such as flecainide, propafenone and ibutilide are awaited with great interest. Further studies are needed to evaluate the efficacy of the oral formulation in the long-term rhythm control.

Bibliography

Papers of special note have been highlighted as:

- of interest
- •• of considerable interest
- Camm AJ, Kirchhof P, Lip GY *et al.* Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology. *Eur. Heart J.* 31(19), 2369–2429 (2010).
- Recent evidence-based practice guidelines on management of atrial fibrillation (AF).
- 2 Go AS, Hylek EM, Phillips KA *et al.* Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) study. *JAMA* 285(18), 2370–2375 (2001).

- 3 Wyse DG, Waldo AL, DiMarco JP *et al.* A comparison of rate control and rhythm control in patients with atrial fibrillation. *N. Engl. J. Med.* 347, 1825–1833 (2002).
- Roy D, Talajic M, Nattel S *et al.* Rhythm control versus rate control for atrial fibrillation and heart failure. *N. Engl. J. Med.* 358, 2667–2677 (2008).
- 5 Gallagher MM, Yap YG, Padula M *et al.* Arrhythmic complications of electrical cardioversion: relationship to shock energy. *Int. J. Cardiol.* 123, 307–312 (2008).
- 6 Nichol G, McAlister F, Pham B et al. Meta-analysis of randomised controlled trials of the effectiveness of antiarrhythmic agents at promoting sinus rhythm in patients with atrial fibrillation. *Heart* 87, 535–543 (2002).

- Dobrev D, Nattel S. New antiarrhythmic drugs for treatment of atrial fibrillation. *Lancet* 375(9721), 1212–1223 (2010).
- Comprehensive review on new antiarrhythmic drugs focusing on their mechanism of action in relationship to AF underlying mechanisms.
- 8 Camm AJ, Savelieva I. New antiarrhythmic drugs for atrial fibrillation: focus on dronedarone and vernakalant. J. Interv. Card. Electrophysiol. 23(1), 7–14 (2008).
- 9 Fedida D, Orth PM, Chen JY et al. The mechanism of atrial antiarrhythmic action of RSD1235. J. Cardiovasc. Electrophysiol. 16, 1227–1238 (2005).
- Explains vernakalant atrial selectivity and clinical efficacy.

Vernakalant hydrochloride in the treatment of atrial fibrillation Review: Clinical Trial Outcomes

- 10 Naccarelli GV, Wolbrette DL, Samii S et al. Vernakalant, a promising therapy for conversion of recent-onset atrial fibrillation. Expert Opin. Investig. Drugs 17, 805-810 (2008).
- 11 Amos GJ, Wettwer E, Metzger F et al. Differences between outward currents of human atrial and subepicardial ventricular myocytes. J. Physiol. (Lond.) 491, 31-50 (1996).
- 12 Dobrev D, Friedrich A, Voigt N et al. The G protein-gated potassium current I(K,ACh) is constitutively active in patients with chronic atrial fibrillation. Circulation 112(24), 3697-3706 (2005).
- 13 Dorian P, Pinter A, Mangat I et al. The effect of vernakalant (RSD1235), an investigational antiarrhythmic agent, on atrial electrophysiology in humans. I. Cardiovasc. Pharmacol. 50, 35-40 (2007).
- 14 Orth PM, Hesketh JC, Mak CK et al. RSD1235 blocks late INa and suppresses early after depolarizations and torsades de pointes induced by class III agents. Cardiovasc. Res. 70(3), 486-496 (2006).
- 15 Sossalla S, Kallmeyer B, Wagner S et al. Altered Na⁺ currents in atrial fibrillation effects of ranolazine on arrhythmias and contractility in human atrial myocardium. J. Am. Coll. Cardiol. 55(21), 2330-2342 (2010)
- 16 Mao ZL, Wheeler JJ, Clohs L et al. Pharmacokinetics of novel atrial-selective antiarrhythmic agent vernakalant hydrochloride injection (RSD1235): Influence of CYP2D6 expression and other factors. J. Clin. Pharm. 49(1), 17-29 (2009)
- 17 Cheng JWM. Vernakalant in the management of atrial fibrillation. Ann. Pharmacother. 42(4), 533-542 (2008).
- 18 Cheng JWM, Rybak I. Pharmacotherapy options in atrial fibrillation: focus on vernakalant. Clin. Med. Therapeutics 1, 215-230 (2009).
- 19 Roy D, Rowe BH, Stiell IG et al. A randomized, controlled trial of RSD1235, a novel antiarrhythmic agent, in the treatment of recent onset atrial fibrillation. J. Am. Coll. Cardiol. 44(12), 2355-2361 (2004).
- 20 Roy D, Pratt CM, Torp-Pedersen C et al. Vernakalant hydrochloride for rapid conversion of atrial fibrillation: a Phase III, randomized, placebo-controlled trial. Circulation 117, 1518-1525 (2008).
- The first Phase III randomized trial on vernakalant efficacy in AF rapid conversion.

- 21 Kowey PR, Roy D, Pratt CM et al. Vernakalant hydrochloride for the rapid conversion of atrial fibrillation after cardiac surgery. A randomized, double-blind, placebo-controlled trial. Circ. Arrhythm Electrophysiol. 2, 652-659 (2009).
- 22 Pratt CM, Roy D, Torp-Pedersen C et al. Usefulness of vernakalant hydrochloride injection for rapid conversion of atrial fibrillation. Am. J. Cardiol. 106, 1277-1283 (2010).
- 23 Stiell IG, Roos JS, Kavanagh KM et al. A multicenter, open-label study of vernakalant for the conversion of atrial fibrillation to sinus rhythm. Am. Heart *J.* 159(6), 1095–1101 (2010).
- 24 Camm AJ, Capucci A, Hohnloser S et al. A randomized active-controlled study comparing the efficacy and safety of vernakalant to amiodarone in recent-onset atrial fibrillation. J. Am. Coll. Cardiol. 57(3), 313-321 (2011).
- The comparative trial between vernakalant and intravenous amiodarone in conversion of recent-onset AF.
- 25 Tian D, Frishman WH. Vernakalant: a new drug to treat patients with acute onset atrial fibrillation. Cardiol. Rev. 19(1), 41-44 (2011).
- 26 Kochiadakis GE, Igoumenidis NE, Hamilos ME et al. A comparative study of the efficacy and safety of procainamide versus propafenone versus amiodarone for the conversion of recent-onset atrial fibrillation. Am. J. Cardiol. 99(12), 1721-1725 (2007).
- Boriani G, Diemberger I, Biffi M et al. 27 Pharmacological cardioversion of atrial fibrillation: current management and treatment options. Drugs 64(24), 2741-2762 (2004).
- 28 Hilleman DE, Spinler SA. Conversion of recent-onset atrial fibrillation with intravenous amiodarone: a meta-analysis of randomized controlled trials. Pharmacotherapy 22, 66-74 (2002).
- Bianconi L, Mennuni M. Comparison 29 between propafenone and digoxin administered intravenously to patients with acute atrial fibrillation. PAFIT-3 Investigators. The Propafenone in Atrial Fibrillation Italian Trial. Am. J. Cardiol. 82(5), 584-588 (1998).
- 30 Kochiadakis GE, Igoumenidis NE, Simantirakis EN et al. Intravenous propafenone versus intravenous amiodarone in the management of atrial fibrillation of recent onset: a placebo-controlled study. Pacing Clin. Electrophysiol. 21, 2475-2479 (1998).

- 31 Alp NJ, Bell JA, Shahi M. Randomised double blind trial of oral versus intravenous flecainide for the cardioversion of acute atrial fibrillation. Heart 84, 37-40 (2000).
- 32 Ellenbogen KA, Clemo HF, Stambler BS et al. Efficacy of ibutilide for termination of atrial fibrillation and flutter. Am. J. Cardiol. 78(8A), 42-45 (1996).
- Gowda RM, Khan IA, Punukollu G et al. 33 Use of ibutilide for cardioversion of recent-onset atrial fibrillation and flutter in elderly. Am. J. Ther. 11(2), 95-97 (2004).
- Hiatt WR, Lincoff AM, Harrington RA. 34 Acute pharmacological conversion of atrial fibrillation to sinus rhythm: is short-term symptomatic therapy worth it? A report from the December 2007 Meeting of the Cardiovascular and Renal Drugs Advisory Committee of the Food and Drug Administration. Circulation 117(22), 2956-2957 (2008).
- 35 Cotter G, Blatt A, Kaluski E et al. Conversion of recent onset paroxysmal atrial fibrillation to normal sinus rhythm: the effect of no treatment and high-dose amiodarone. A randomized, placebocontrolled study. Eur. Heart J. 20(24), 1833-1842 (1999)
- Vardas PE, Kochiadakis GE, Igoumenidis 36 et al. Amiodarone as a first-choice drug for restoring sinus rhythm in patients with atrial fibrillation: a randomized, controlled study. Chest 117(6), 1538-1545 (2000).
- 37 Donovan KD, Dobb GJ, Coombs LJ et al. Reversion of recent-onset atrial fibrillation to sinus rhythm by intravenous flecainide. Am. J. Cardiol. 67(2), 137-141 (1991).
- Madrid AH, Moro C, Marin-Huerta E et al. 38 Comparison of flecainide and procainamide in cardioversion of atrial fibrillation. Eur. Heart J. 14, 1127-1131 (1993).
- Fresco C, Proclemer A, Pavan A et al. 39 Intravenous propafenone in paroxysmal atrial fibrillation: a randomized, placebo-controlled, double-blind, multicenter clinical trial. Paroxysmal Atrial Fibrillation Italian Trial (PAFIT)-2 investigators. Clin. Cardiol. 19(5), 409-412 (1996).
- Reisinger J, Gatterer E, Lang W et al. 40 Flecainide versus ibutilide for immediate cardioversion of atrial fibrillation of recent onset. Eur. Heart J. 25, 1318-1324 (2004).
- Volgman AS, Carberry PA, Stambler B et al. 41 Conversion efficacy and safety of intravenous ibutilide compared with intravenous procainamide in patients with atrial flutter or fibrillation. J. Am. Coll. Cardiol. 31(6), 1414-1419 (1998).

Review: Clinical Trial Outcomes Marinelli, Ciccarelli & Capucci

- 42 Stambler BS, Wood MA, Ellenbogen KA et al. Efficacy and safety of repeated intravenous doses of ibutilide for rapid conversion of atrial flutter or fibrillation. Ibutilide Repeat Dose Study investigators. Circulation 94(7), 1613-1621 (1996).
- 43 Martínez-Marcos FJ, García-Garmendia JL, Ortega-Carpio A et al. Comparison of intravenous flecainide, propafenone, and amiodarone for conversion of acute atrial fibrillation to sinus rhythm. Am. J. Cardiol. 86(9), 950-953 (2000).
- Gowda RM, Khan IA, Punukollu G et al. 44 Female preponderance in ibutilide-induced torsade de pointes. Int. J. Cardiol. 95(2-3), 219-222 (2004)

Websites

- 101 US FDA, Center for Drug Evaluation and Research. Minutes of the meeting of the Cardio-Renal Advisory Committee, 14 November 2007. www.fda.gov/ohrms/dockets/ac/07/briefing/ 2007-4327b1-02-fda-backgrounder.pdf (Accessed 12 December 2010)
- 102 Astellas Pharma US, Inc. Kynapid, Vernakalant hydrochloride injection. NDA 22-034. www.fda.gov/ohrms/dockets/ac/07/ briefing/2007-4327b1-01-astellasbackgrounder.pdf (Accessed 12 December 2010)
- 103 A Phase IIIb study of vernakalant injection in patients with recent onset symptomatic atrial fibrillation (ACT V). http://clinicaltrials.gov/ct2/show/NCT0098 9001?term=vernakalant&rank=3 (Accessed 10 December 2010)

- 104 Cardiome Pharma Corp. www.cardiome.com/VernakalantOral.php (Accessed 10 December 2010)
- 105 European Medicine Agency Assessment Report for Brinavess. www.ema.europa.eu/docs/en_GB/ document_library/EPAR_-_Public_ assessment_report/human/001215/ WC500097150.pdf (Accessed 12 December 2010)
- 106 Cardiome. Cardiome announces suspension of enrollment in ACT 5 trial, 21 October 2010. http://cardiome.com/wordpress/?p=563 (Accessed 12 December 2010)