Implementing the use of Vernakalant

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Vernakalant

- Class I and III antiarrhythmic
- Blocks sodium and potassium channels in all phases of the action potential \(^{(2)}\)
- Atrial-specific
- Pharmacological cardioversion of recent onset AF \(^{(3)}\)
- Post marketing use in AF < 48 hours duration
- Half life 2-3 hours (5.5 hours in poor metabolisers) \(^{(4)}\)

Licensed for the rapid conversion of recent-onset AF to SR in adults who are non-surgery patients with AF ≤ 7 days duration or post-cardiac surgery patients with AF ≤ 3 days duration \(^{(1)}\)
Action during AF

Normal  ____  
AF  _____

ATRIUM  
600-1000 BPM

VENTRICLE  
100-160 BPM

During Vernakalant infusion

Shortened Refractory Period  
Prolongation of Refractory Period

Minor prolongation of Refractory Period  
(QRS & QT)
<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>n=</th>
<th>AF duration</th>
<th>Time to conversion (median)</th>
<th>Conversion to SR vs placebo or control</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACT I (2008)</td>
<td>Double blind, placebo controlled</td>
<td>336</td>
<td>3h – 45 days</td>
<td>11 mins</td>
<td>51.7% vs 4%</td>
</tr>
<tr>
<td>ACT II (2009)</td>
<td>Double blind, placebo controlled</td>
<td>160</td>
<td>3 – 72h</td>
<td>12 mins</td>
<td>47% vs 14%</td>
</tr>
<tr>
<td>ACT III (2010)</td>
<td>Double blind, placebo controlled</td>
<td>265</td>
<td>3h – 45 days</td>
<td>8 mins</td>
<td>51.2% vs 3.6%</td>
</tr>
<tr>
<td>ACT IV (2010)</td>
<td>Open label</td>
<td>167</td>
<td>3h – 45 days</td>
<td>14 mins</td>
<td>50.9%</td>
</tr>
<tr>
<td>AVRO (2011)</td>
<td>Double blind, active controlled</td>
<td>232</td>
<td>3 – 48h</td>
<td>11 mins</td>
<td>51.7% vs 5.2%</td>
</tr>
<tr>
<td>CRAFT (2004)</td>
<td>RCT, double blind</td>
<td>56</td>
<td>3-72h</td>
<td>14 mins</td>
<td>61% vs 5% (within 30 min)</td>
</tr>
<tr>
<td>SCENE2 (2012)</td>
<td>RCT, double blind</td>
<td>54</td>
<td>Atrial flutter</td>
<td>3h – 45 days</td>
<td>3% vs 0%</td>
</tr>
</tbody>
</table>
Contemporary evidence

**Vernakalant vs Flecainide (2017)** \(^{(12)}\)
Non-randomised, retrospective study, n=100 each group
Endpoint – conversion to SR within 120 minutes
67% vs 46%
Vernakalant group discharged earlier

**Vernakalant vs Electrical Cardioversion (2017)** \(^{(13)}\)
Retrospective study, n=197 vernakalant group vs n=199 electrical cv group
Endpoint – AF onset to initiation of treatment and to restoration of SR
SR restoration 66.5% vs 94%
Vernakalant group discharged sooner and lower rates of AF recurrence at 1 yr FU (36 % vs 63%)

**Real world comparison in the ED and after cardiac surgery (2017)** \(^{(14)}\)
79% converted in the ED group and 74% post cardiac surgery, majority with first infusion
Median conversion time 16 minutes, effectiveness similar in both groups
Maintenance of SR at 7 days
Recent onset AF

Yes

Haemodynamic instability?

No

Elective

Patient choice

Pharmacological cardioversion

Severe HFrEF, significant aortic stenosis

Electrical cardioversion (IB)

Intravenous Amiodarone (IA)

Intravenous Vernakalant (IIB)

Coronary artery disease, moderate HFrEF or HFmrEF/HFpEF, abnormal LVH

Amiodarone (IA)

Intravenous Flecainide (IA)

Intravenous Ibutilide (IIaB)*

Intravenous Propafenone (IA)

No relevant structural heart disease

Pill in the pocket Flecainide (IIaB)

Propafenone (IIaB)

Urgent

AF = atrial fibrillation; HFmrEF = heart failure with mid-range ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; LVH = left ventricular hypertrophy.

*Ibutilide should not be used in patients with long QT interval.
Who qualifies?

• AF onset of < 48 hours duration
• Haemodynamically stable and absence of severe aortic stenosis, SBP <100mmHg and heart failure class NYHA III or IV
• No ACS within 30 days
• Need to know when the onset of symptoms developed
• Be in a monitored environment (DC cardioversion available)
• Adequately hydrate to haemodynamically optimise the patient
• Correct potassium if <3.5mmol/L
• Checklist
Contraindications (checklist)

<table>
<thead>
<tr>
<th>Question</th>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Does the patient have heart failure class NYHA III or NYHA IV?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Has the patient presented with an acute coronary syndrome (including myocardial infarction) in the last 30 days?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Does the patient have severe aortic stenosis?</td>
<td></td>
<td></td>
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<tr>
<td>Does the patient have a systolic blood pressure &lt; 100 mm Hg?</td>
<td></td>
<td></td>
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<tr>
<td>Does the patient have prolonged QT interval at baseline (uncorrected &gt; 440 msec)?</td>
<td></td>
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<tr>
<td>Does the patient have severe bradycardia, sinus node dysfunction or second and third degree heart block, in the absence of a pacemaker?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Has the patient received an intravenous rhythm control antiarrhythmic drug (class I and/or class III) within 4 hours of the time when BRINAVESS will be infused?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Does the patient have hypersensitivity to the active substance or to any of the excipients?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Do NOT give other IV antiarrhythmic drugs for at least 4 hours after infusion of BRINAVESS.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Cautions

• Not recommended for patients with:
  • LVEF <35%
  • Hypertrophic obstructive cardiomyopathy, restrictive cardiomyopathy or constrictive pericarditis
  • Class I or III intravenous anti-arrhythmics between 4 and 24 hours prior to use (lack of data)
  • Advanced hepatic impairment
  • Clinically meaningful valvular stenosis
Preparation

• Intravenous in a monitored environment
• Baseline observations (throughout infusion and for at least 15 minutes after)
• Continuous cardiac monitoring and electrical cardioversion available
• Checklist
• Adequately hydrated and haemodynamically optimised
• Correct hypokalaemia to >3.5mmol/L
• Low molecular weight heparin (or OAC if pre-existing)

INJECT, CONVERT, DISCHARGE
Administration

• Dilute to a concentrate of 4mg/ml (0.9% sodium chloride or 5% glucose)
• Dose calculated according to weight
  • \( \leq 100 \text{kg} \): 25ml of vernakalant 20mg/ml is added to 100ml of diluent
  • \( \geq 100 \text{kg} \): 30ml of vernakalant 20mg/ml is added to 120ml of diluent
• 1\textsuperscript{st} infusion 3mg/kg over 10 minutes

\[\text{SR} \rightarrow \text{AF or atrial flutter}\]

Continue infusion until complete then stop

2\textsuperscript{nd} infusion 2mg/kg over 10 minutes

\[\text{SR} \rightarrow \text{AF or atrial flutter}\]

Continue infusion until complete then stop

Consider alternatives *
Observations

• Observe for adverse signs (even after administration)
• Hypotension, bradycardia, atrial flutter, ventricular arrhythmia
• Hypotension more likely in patients with CHF (16.1% v 4.7%)
• Ventricular arrhythmias more likely in CHF patients (7.3% v 1.3%) (16)
• STOP infusion if any adverse signs develop (and DO NOT give 2\textsuperscript{nd} infusion)
• Valvular heart disease – watch closely (higher incidence of ventricular arrhythmias)
• Further monitoring for 2 hours after the start of infusion and until clinical and ECG parameters stable (due to AE’s)
## Adverse effects

<table>
<thead>
<tr>
<th>Very common</th>
<th>Common</th>
<th>Uncommon</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dysgeusia</td>
<td>Dizziness</td>
<td>Vasovagal syncope</td>
</tr>
<tr>
<td>Sneezing</td>
<td>Headache</td>
<td>Eye irritation</td>
</tr>
</tbody>
</table>
<pre><code>                             | Bradycardia                | Visual impairment          |
                             | Hypotension                | Sinus arrest               |
                             | Cough                      | Complete AV block          |
                             | Nausea                     | LBBB / RBBB               |
                             | Vomiting                   | VT                        |
                             | Pruritis                   | VE’s                      |
                             |                            | Prolonged QT               |
                             |                            | Flushing                   |
                             |                            | Dyspnoea                   |
                             |                            | Diarrhoea                  |
                             |                            | Infusion site irritation    |
</code></pre>
Local application

• HRC, Professor Camm’s presentation
• Discussion with cardiologist
• Review of the evidence
• Drugs and Therapeutics Committee application and presentation (2014)
• Obstacles…. Sourcing the drug
• Re-presented to DTC and approved
• Policy, pathway, communication
• Local education
• In use! Initial use very promising.....
Initial findings...

- Early days ... used in 8 patients and 100% success
- Emergency Department use
- No AE’s
- No discontinuation necessary (close attention to the checklist)
- Strictly according to protocol
- Median time to conversion = 17 mins
- Patient perception
- No AF recurrence at FU (4 weeks)
Case study 1

- 29 year old, ex-navy, admitted 4.7.17, new onset AF
- No co-morbidities, palpitations previously, never documented
- Grandfather died in his 20’s of a cardiac event – diagnosis unclear
- HR 42-64bpm, BP 117/74mmHg, no adverse signs, bloods stable
- Echo showed structurally normal heart
- Received PO Bisoprolol night before
- Symptomatic, breathless at rest, anxious, chest discomfort, palpitations
- EAU so moved to monitored bed in HDU
• 3mg/kg of diluted solution, 10 mins, remained in rate controlled AF
• 15 minutes wait, stable throughout, cannula site discomfort and mild sneezing
• 2\textsuperscript{nd} infusion, 2mg/kg, 10 mins, last minute of infusion reverted to SR!
• Well, monitored for 2 hours, discharged with OAC, OPA in 2/52
Case study 2

• 75 year old, female
• PMH hypertension, PAF, angiogram 2014 (normal)
• Sudden onset of palpitations, HR 130’s, BP 158/86mmHg
• Already on Apixaban, anti-hypertensives, statin
• Echo (normal)
• Rate controlled with IV Metoprolol 5mg (HR 136 to 106)
• 3mg/kg vernakalant over 15 minutes, reverted at 7 minutes
• Continued meds
• Home after 2 hours
• FU at 4 weeks, SR with no further episodes
What next?

• Widening the use
• Sharing of protocols
• Local audit
• Ongoing communication
• Publication

Belfast, Cardiology and ED
Leeds
Norwich
Basildon
Harlow, Essex
Kings College, London
Royal Free, London
The Lister, London
References


