Rational Approach to Improving Cardiac Arrhythmia Therapy

Stanley Nattel, MD

DEDICATED TO THE MASTER OF RATIONAL THERAPEUTICS

SENAC: Cinchona bark for palpitations (1749)

FREY: On atrial fibrillation in humans and Its Elimination by Quinidine (1918)

Ventricular fibrillation as an electrical accident

Lidocaine to treat ventricular ectopy post-MI

A

B

C

WIGGERS CJ, Am Heart J 20:399-412, 1940

GIANELLY R et al, NEJM 277:1215-1219, 1967
Total suppression of ventricular arrhythmias by encainide


Oral flecainide acetate for the treatment of ventricular arrhythmias


Odds ratio for total mortality 1-48 hr post-MI


Effects of class 1C antiarrhythmias on post-MI mortality

CAST


CAST II


CAST II Investigators, NEJM 327:227-233, 1992

Effects of class 1C antiarrhythmias on post-MI mortality

CAST


CAST II


CAST II Investigators, NEJM 327:227-233, 1992
Meta-analysis of quinidine effects on mortality in AF patients

OK, Class I drugs are bad. Class III is the future.

Effects of a pure class III drug on post-MI mortality

Something doesn’t fit!

Focus on a specific arrhythmia

Age-Related Prevalence of AF
New antiarrhythmic drug development approaches for AF

Novel ion channel targets

Problem of ventricular proarrhythmia

………. and strategy of atrial-selective therapies

Atrial-selective therapies

$I_{Kur}$ (ultrarapid delayed rectifier) is Atrial-specific in Man

K$^+$ channel blockers with atrial selectivity
**I_{Kur} (ultrarapid delayed rectifier) is Atrial-specific in Man**

**Efficacy of an I_{Kur} blocker (Xen-D0101) on atrial and ventricular ERPs in AT-remodeled dogs**

**Efficacy of an I_{Kur} blocker (Xen-D0101) on AF in dogs with atrial tachycardia remodeling**

**New antiarrhythmic drug development approaches for AF**

**Targeting the substrate**

**Determinants of Arrhythmia Mechanisms in AF: Role of Remodeling**

**Determinants of Arrhythmia Mechanisms in AF: Prevention of Remodeling**
Effects of electrically maintained AF on spontaneous AF maintenance when stimulation stopped

Atrial Myocyte Adaptation to Ca²⁺ Loading

Sinus rhythm (60/min) → 10-fold rate increase → AF (400-600/min) → Cellular Ca²⁺ loading → Threat to cell viability → ICa inactivation → ↓ ICa

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Superiority of Amiodarone in AF


Kochevarakis et al., Heart 2000; 84: 251-257
Effects of Antiarrhythmic Drugs on AF

Effects of Remodeling on $\alpha_{1c}$ Subunit Expression

**SN.2003**

**EF** duration (s)

Vulnerability (%)

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Effects of Various Agents on Cav1.2 Expression

Can we identify new antiarrhythmic approaches that work by preventing atrial-tachycardia remodeling?

Remodeling Induces Two Clinically Relevant AF Substrates: Atrial-tachycardia Remodeling and Structural Remodeling

CHF produces a structural substrate for AF
Can Inhibiting Ang-II Formation Prevent Development of the Substrate for AF?

\[
\begin{array}{c|cccc}
\% \text{ Connective tissue} & \text{AF duration (s)} \\
\hline
\text{CTL} & 0 & ** & ** & ** \\
\text{CHF} & 15 & 700 & 300 & 200 \\
\text{CHF+HI} & 12 & 800 & 500 & 400 \\
\text{CHF+E} & 10 & 900 & 600 & 500 \\
\end{array}
\]

\[L_{i} 	ext{ et al., Circulation 104: 2608-2614, 2001}\]

\(L_{i} \text{ et al., Circulation 104: 2608-2614, 2001}\)

\(c = \text{enalapril, } HI=\text{hydralazine/isosorbide}\)

CHF induces fibrosis and increases AF duration.

Enalapril attenuates fibrosis and AF duration increases.

Can Inhibiting Ang-II Formation Prevent Development of the Substrate for AF?

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\begin{array}{c|cccc}
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Vasodilator therapy does not mimic enalapril effects.

ACE antagonism and clinical AF in LV dysfunction

AF in post-MI patients with LVD

AF in SOLVD patients

\[\text{Pedersen et al., Circulation 1999; 100: 376-380}\]

\[\text{Vermes et al., Circulation 2003; 107: 2926-2931}\]

New antiarrhythmic drug development approaches for AF

Substrate-selective ion channels

Atrial tachycardia remodeling: AF Begets AF


\[\text{SN I.2001}\]
Atrial tachycardia remodeling: AF Begets AF

Constitutive I_{K_ACh} that is enhanced by atrial tachycardia

Effects of I_{K_ACh} block on APD and tachyarrhythmia

Effects of I_{K_ACh} block on APD and tachyarrhythmia

Effects of an I_{K_ACh}-selective blocker (NIP 151) on AF in two canine models

Atrial-selective therapies

I_{K_ACh}

Effects of an I_{K_ACh}-selective blocker (NIP 151) on AF in two canine models
**Effects of an I\textsubscript{Kach}-selective blocker (NIP 151) on AF in two canine models**

<table>
<thead>
<tr>
<th>compound</th>
<th>dose (µg/kg/min)</th>
<th>NO. terminated</th>
<th>AF termination (sec)</th>
<th>plasma conc. (ng/ml)</th>
<th>prevention of AF reinduction</th>
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<td>5</td>
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<td>575±4.25</td>
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*Collateral effects on extra-atrial (SAN) and extracardiac (GI and GU systems) need to be avoided*

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<thead>
<tr>
<th>compound</th>
<th>dose (mg/kg)</th>
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<th>time (sec)</th>
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<td>3/3</td>
<td>55</td>
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**We have come a long way…**

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**…But we do hope to get there!**