The quest for an anti-arrhythmic drug against atrial fibrillation that combines efficacy with safety

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This editorial refers to ‘The combined ion channel blocker AZD1305 attenuates late Na current and Ikur-induced action potential prolongation and repolarization instability’ B. Andersson et al., on page 1003

There is a long history at AstraZeneca to succeed in developing an anti-arrhythmic agent that can safely and effectively restore and maintain sinus rhythm in atrial fibrillation (AF) patients.1–7 For that purpose, the company developed agents that shared the property to suppress the rapid component of the delayed rectifier current (I_{Kr}, Table 1). These drugs prolong repolarization quantified as QT times in vivo or as duration of the action potential (APD) in vitro and are classified as Class III anti-arrhythmics. This strategy is effective against AF, but carries the risk of ventricular pro-arrhythmia, meaning that the drugs may be unsafe. With time proceeding, I_{Kr} block was accompanied in the properties of the drug by inhibiting effects on other ion currents, especially the L-type calcium current (I_{CaL}) and both the peak and the late sodium current (I_{Na} and I_{Na late}, respectively). This combined ion channel block, by preventing the occurrence of early afterdepolarizations (EADs) and spatial dispersion of repolarization, would lead to protection against Torsade de Pointes (TdP) pro-arrhythmia, while maintaining the high efficacy against AF. These pro-arrhythmic activities are often evoked by the short–long–short sequence explaining why Andersson et al.1 included dynamic adaptation of APD using cycle length changes mimicking the short–long–short sequence in their paper published. But let me tell the story.

It started off with almokalant,2,3,8 a rather specific blocker of I_{Kr}. Because this agent induced TdP in a number of patients enrolled in early clinical trials, the drug was withdrawn from further clinical development.9 However, research at AstraZeneca to identify novel agents as well as exploring mechanisms underlying drug-induced repolarization-related pro-arrhythmia continued. Nice examples are the relevance of the infusion rate for almokalant-induced TdP and investigations in which different anti-arrhythmic drugs were combined with almokalant to reduce its potential to induce EADs and TdP.2,3

In the previous study, triggered by a clinical case of TdP in a patient unintentionally administered almokalant at twice the intended rate, it was demonstrated that slow infusion, albeit causing greater increases in QT in time, considerably reduced pro-arrhythmia (1/8 vs. 9/10) in the methoxamine-sensitized rabbit model.2 This indicated the relevance of the speed of drug administration for TdP development.

In the second category, drugs such as: (i) lidocaine,3 a drug that blocks I_{Na} and, more recently, was described to also block I_{Na late} in a ratio of 1:3, (ii) the I_{CaL} blockers nisoldipine and flunarizine, and (iii) ryanodine, a blocker of the sarcoplasmic reticulum Ca^{2+} release channel were combined with almokalant to prevent pro-arrhythmia. Recently, it has been shown that the I_{CaL} blocker flunarizine also blocks I_{Kr} and I_{Na late} without affecting the peak I_{Na} current.10 Lidocaine administered at low and high doses was demonstrated to dose-dependently reduce almokalant-induced TdP with a total TdP prevention with the high dose (0/8) in the methoxamine-sensitized rabbit model of TdP. This protective effect of lidocaine did not reflect in the QT-time, which still increased considerably with almokalant.3 Similar results were seen with the other agents investigated that interfere with Ca-handling.

Logically, the first new anti-arrhythmic drug of AstraZeneca to be tested was a multiple ion channel blocker (Table 1): H345/52 that added I_{CaL}-blocking properties to the regular I_{Kr} antagonism.4 On the basis of non-clinical findings in Purkinje fibres and ventricular myocytes, Langendorff perfused hearts, and in the methoxamine-sensitized rabbit, an agent markedly delaying myocardial repolarization without inducing repolarization-related pro-arrhythmia seemed to be found. However, although no cases of TdP were reported in ∼350 AF patients exposed to H345/52, poor bioavailability and a low efficacy in restoring sinus rhythm halted further clinical development.

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The third drug that underwent clinical testing was AZD7009 which was discontinued from further development for non-cardiovascular reasons. This multiple ion-channel blocker affecting $I_{Kr} + I_{Na}$ (Table 1) seemed highly effective: conversion rates for terminating AF lasting 1 month was over 80%. In the methoxamine-sensitized rabbit model, no TdP was seen: the terminating AF lasting 1 month was over 80%. In the trials. Nevertheless, I admire their persistence and determination.

Combining block of multiple ion channels may therefore be of great interest to find an ideal anti-arrhythmic drug. On the other hand, safety and effectiveness may also be warranted with drugs that electrophysiologically affect the atria more prominently than the ventricle: atrial-specific drugs. More recently, it has been suggested that $I_{Na}$ block as is achieved with ranolazine and vernakalant is more effective in the atria.

Did they succeed at AstraZeneca: not yet. AZD1305 was recently withdrawn because of signs of pro-arrhythmia in clinical trials. Nevertheless, I admire their persistence and determination.

Therefore, I hope that they will succeed and wish them all the best in these efforts.

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Table 1 Overview of drugs developed by AstraZeneca

<table>
<thead>
<tr>
<th>Drug</th>
<th>Name</th>
<th>Ion currents blocked</th>
<th>IC 50 (µM/L)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>H234/09</td>
<td>Almokalant</td>
<td>$I_{Kr}$</td>
<td>50 nM</td>
<td>Carmeliet et al.</td>
</tr>
<tr>
<td>H345/52</td>
<td></td>
<td>$I_{Kr} + I_{CaL}$</td>
<td>40 nM + 1.3</td>
<td>Amos et al.</td>
</tr>
<tr>
<td>AZD7009</td>
<td></td>
<td>$I_{Kr} + I_{Na}$</td>
<td>0.6 + 4.3</td>
<td>Person et al.</td>
</tr>
<tr>
<td>AZD1305</td>
<td></td>
<td>$I_{Kr} + I_{CaL} + I_{Na}$</td>
<td>8 + 11 (1:1)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>$I_{Na}$</td>
<td>0.4 + 1.2 + 1.5</td>
<td>Carlsson et al. and Andersson et al.</td>
</tr>
</tbody>
</table>

References