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Pharmacology and Toxicology of Nav1.5-Class 1 anti-arrhythmic drugs

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SYNOPSIS

Although cardiac sodium channel blocking drugs can exert antiarrhythmic actions, they can also provoke life-threatening arrhythmias through a variety of mechanisms. This review addresses the way in which drugs interact with the channel, and how these effects translate to clinical beneficial or detrimental effects. A further understanding of the details of channel function and of drug-channel interactions may lead to the development of safer and more effective antiarrhythmic therapies.

Keywords

sodium channel; drugs; proarrhythmia

LEARNING FROM HISTORY

It is said that the mid-18th century French physician Jean-Baptiste de Sénac was the first to document an antiarrhythmic effect of the bark of the cinchona plant. Almost exactly a century ago, Wenckebach encountered a patient with atrial fibrillation who reported he could abort his attacks by using quinine, extracted from cinchona plant bark. Quinidine, an isomer of quinine, was subsequently developed as an antiarrhythmic and widely used for decades. Quinidine is a “mixed” antiarrhythmic, with prominent sodium channel blocking (as well as potassium channel blocking) properties. Quinidine is not widely used for many reasons: treatment carries a risk of potentially fatally adverse effects, including thrombocytopenia and torsades de pointes; most patients will develop gastrointestinal side effects which can become intolerable; and the drug is no longer under patent and so not commercially promoted. The first few decades of the 20th century saw the introduction of other antiarrhythmic agents, most developed from initial drug structures identified as depressors of conduction or contractile function in nerve or cardiac muscle preparations.

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These included lidocaine, which because of near-complete first pass metabolism can only be used intravenously, and procainamide and disopyramide, drugs that, like quinidine, can be antiarrhythmic but are poorly tolerated because of the high incidence of proarrhythmia and other adverse effects.

The arrival of better tolerated drugs

The 1970s saw the recognition that frequent ventricular ectopic beats, particularly in patients with known structural heart disease such as myocardial scarring, constitute a risk factor for sudden cardiac death (SCD), and therefore an interest in suppressing these ectopics. New antiarrhythmic drugs that were better tolerated than available drugs became available, and virtually all share the property that they inhibit cardiac sodium current.

One avenue to development of these new drugs was manipulation of the lidocaine structure to result in congeners with similar electrophysiologic properties but pharmacokinetic profiles that allowed chronic oral dosing. Mexiletine is one such congener that continues to be used, while others (such as tocainide) have been withdrawn because of a risk for non-cardiovascular toxicities.

Another group of sodium channel blockers that became available for clinical investigation in the late 1970s was the “class Ic” subgroup (this designation is discussed further later in this article). The first two members of this class to be introduced into clinical investigation and subsequently marketed were encainide and flecainide. Initial clinical trials of these agents highlighted several unusual properties, some of which appeared to make them desirable as antiarrhythmic agents.[1–4] The most prominent of these was that the drugs could suppress ventricular ectopic beats without producing any of the non-cardiovascular toxicities (gastrointestinal symptoms, drug induced lupus syndrome, etc.) that characterized drugs available at the time. In patients with pre-excitation, the drugs could result in prompt disappearance of a delta wave, an initial clue to potential antiarrhythmic activity in this setting.

Encainide did have unusual pharmacokinetic properties: its antiarrhythmic effects appear to be mediated by biotransformation to active metabolites, and this metabolism is accomplished by the cytochrome P450 *CYP2D6;* 5–10% of patients Caucasians and African subjects lack CYP2D6 activity and therefore when exposed to encainide do not generate the active metabolites and thus display little or no antiarrhythmic effect.[5] Flecainide, on the other hand, appeared to lack this pharmacokinetic drawback and unlike most other antiarrhythmics available at the time could be administered twice daily. In fact, flecainide is a *CYP2D6* substrate, but is also cleared by renal excretion of unchanged drug; therefore, the *CYP2D6* polymorphism does not affect flecainide dosing except in rare individuals who are poor metabolizers and who have renal dysfunction.

Thus, the development of encainide and flecainide appeared to herald a new era in which arrhythmias could be readily suppressed by drugs that were well tolerated. One feature of treatment with these agents was that arrhythmia suppression was routinely accompanied by obvious and striking prolongation of P wave, PR interval, and QRS durations, evidence of marked conduction slowing across the heart. Such ECG changes had been seen with the

aggressive use of high dose of quinidine to convert atrial fibrillation,[6] where they were considered a sign of drug toxicity, occasionally preceding the development of ventricular tachycardia (VT). Even during the early development of encainide and flecainide, case reports emerged that occasional patients appeared to develop “paradoxical” worsening of ventricular arrhythmias, including patients who developed incessant sustained monomorphic or polymorphic VT, some of whom who could not be resuscitated.[7] This appeared to occur primarily in patients in whom the presenting arrhythmia was sustained monomorphic VT.

The Cardiac Arrhythmia Suppression Trial (CAST)

The conventional wisdom in the 1980s was that ventricular ectopic activity represented a marker identifying individuals at increased risk for sudden cardiac death, and a commonly-adopted therapeutic approach in the cardiovascular community was to attempt to suppress ventricular ectopic beats to reduce the risk for SCD. Accordingly, the National Hearth Lung and Blood Institute (NHBLI) launched a series of studies in the 1980s designed to rigorously test the concept that suppressing ventricular ectopic activity using newly-introduced and well-tolerated agents, such as encainide and flecainide, could impact the important public health problem of SCD. The Cardiac Arrhythmia Pilot Study (CAPS) showed that such a trial was feasible and identified no major safety concerns.[8] In follow-up, NHLBI launched the Cardiac Arrhythmia Suppression Trial (CAST) in 1987. CAST was a double-blind, placebo-controlled, randomized trial in patients with ventricular ectopic activity six days to two years following a myocardial infarction. Because the proarrhythmia risk had been recognized, only patients with ejection fractions >30% were eligible. The trial was halted prematurely in the spring 1989 when a planned interim data analysis revealed a striking excess of death among patients treated with encainide or flecainide, compared to those randomized to placebo.[9] A third drug, moricizine, continued to be tested in CAST-II, but this also did not reduce SCD and may have increased it.[10,11]

CAST was a landmark clinical trial for many reasons. *First*, was that it showed the power of the randomized clinical trial to unambiguously determine drug actions in a complex clinical setting, by comparison to placebo. *Second*, it had the obvious effect of bringing all sodium channel blocker-related antiarrhythmic drug development to a screeching halt; the drug development world then turned to action potential prolongation, largely accomplished by block of I_{Kr}, and this strategy, in turn, has also been plagued by proarrhythmia. Importantly, none of these drugs were developed at a time when the molecular basis for drug-channel interactions was not well-understood, and the mechanisms underlying proarrhythmia of various types were just beginning to be defined. Thus, the CAST result raised important questions regarding the fundamental mechanisms whereby sodium channel blocking drugs act at the molecular, cellular, and whole organ levels to promote or suppress arrhythmias.

IN VITRO MECHANISMS OF SODIUM CHANNEL BLOCKING DRUG ACTION

The initial studies by Hodgkin and Huxley in the squid giant axon generated a formal mathematical description of sodium channel transitions from closed to open to inactivated and then recovery to rest states (gating) as a function of voltage.[12, 13] The first sodium channel was cloned from the electric eel electroplax in the early 1980s[14] and the inferred structure showed that the now familiar model, present in all mammalian voltage-gated

sodium channels including the predominant human cardiac isoform *SCN5A*,[15] of four domains each consisting of six membrane spanning segments, with S4 acting as the voltage sensor. Molecular and mathematical models have provided valuable tools with which to dissect the mechanisms whereby drugs inhibit sodium current. As discussed below, the question of how such block translates into antiarrhythmic or proarrhythmic clinical actions is actually less well understood.

Sub-classifying drugs

With the development of multiple sodium channel blocking antiarrhythmics came the hope that classifying drugs by their fundamental electrophysiologic properties might be useful in understanding their basic mechanisms of action, targeting specific drugs to specific patients or arrhythmia mechanisms, and directing new drug development. A first attempt at such a classification divided sodium channel blocking drugs into those that prolong cardiac action potentials (quinidine, procainamide, disopyramide), and those that have little effect on action potentials or in fact shortened them slightly (lidocaine and congeners). We now recognize that drugs of the first type prolong action potentials by inhibiting cardiac potassium currents, while drugs of the second type may shorten action potential by inhibiting the persistent or “late” sodium current discussed further below.

Initial studies in nerve[16] and subsequently in cardiac tissue[17] demonstrated that a striking feature of the interaction between drugs and sodium channels was that drug effects are time- and voltage-dependent. Thus, for example, lidocaine showed little block of cardiac sodium current (assessed as maximum upstroke slope of phase 0 of action potentials in initial experiments) when the preparation was well polarized and driven slowly. By contrast, block was prominent in depolarized preparations or those driven rapidly. These observations led Hille[18] and Hondeghem and Katzung[19] to propose the “modulated receptor hypothesis”: they postulated that blocking drugs bound to and unbound from a specific “receptor” on cardiac sodium channels and that this binding and unbinding was determined by specific rate constants that were, themselves, state dependent. Thus, for example, some drugs associate with and dissociate from the inactivated state much more avidly than with the rest or open states.

At roughly the same time, Campbell and Vaughn-Williams noted that antiarrhythmic drugs exerted strikingly diverse effects on sodium current (again measured as maximum phase 0 upstroke slope) when rapid pacing was initiated in a quiescent guinea pig papillary muscle. For virtually all drugs, the first upstroke slope was near-identical to that recorded in non-drug treated preparations: this result indicates that most drugs evaluated had little affinity for the resting state. For lidocaine and mexiletine, the onset of drug block was very rapid, occurring within a beat or two, while with encainide, the onset was very slow, taking tens of beats; quinidine and disopyramide were intermediate.[20–22] Recovery from drug block, assessed by recording maximum upstroke slope after trains of rapid pacing were interrupted for variable periods of time, also varied among drugs, fastest for lidocaine and slowest for encainide. These properties define “use-dependence”, i.e. block develops as the channel is used, becomes more intense as the channel is used more (i.e. at faster rates), and resolves when the channel is at rest. Based on these data, they proposed the now widely used

terminology of “class Ia” for quinidine and disopyramide; “class Ib” for lidocaine and mexiletine; and “class Ic” for encainide and flecainide.[20, 23] Interpreted in the modulated receptor hypothesis framework, drugs such as lidocaine bind rapidly to their receptor in either the open or inactivated state, and similarly unbind rapidly. By contrast, class Ic drugs bind slowly, and dissociate slowly. As a result, drugs such as lidocaine produce little sodium channel block in normal tissues driven at slow rates, whereas encainide and flecainide produce prominent steady state sodium channel block even in normal tissue driven at slow rates. This interpretation, then, explains the striking increases in ECG intervals such as QRS duration observed during the earliest clinical trials of class Ic drugs.

Where is the receptor?

The cloning of sodium channels, including the cardiac sodium channel, was followed by studies to identify the molecular determinants of toxin and drug binding to the channel. An elegant series of site-directed mutagenesis studies over 20 years ago identified a single extracellular residue in domain I as critical for determining sensitivity to the blocking toxin tetrodotoxin (TTX): the presence of a cysteine in the cardiac isoform renders the sodium channel relatively resistant to TTX block, while the presence of a tyrosine in the corresponding position in nerve channels (or by site-directed mutagenesis in the cardiac channel) renders the channel TTX sensitive.[24, 25]

Mutagenizing a phenylalanine residue to alanine in the cytoplasmic aspect of the S6 segment of domain IV in nerve channels eliminated local anesthetic block, thus implicating this site as a receptor for blocking drugs,[26] and subsequent studies have also implicated aromatics in the cytoplasmic aspect of S6 in other domains.[27, 28] Multiple pathways have been described whereby drugs access such receptor sites: from the cytoplasm, though the pore from the outside, or through side pores on the channel.[29, 30] Taken together, the molecular data support the initial view[18, 19] that the voltage and use-dependence of block by antiarrhythmics (or for blockers of other sodium channel isoforms such as local anesthetics or anticonvulsants) can be understood as voltage-dependent changes in channel structure that modulate accessibility of the drug binding site to drug, dissociation of the drug from the binding site, and specific affinity of the drug for the binding site.

Multiple mechanisms have been proposed to explain how drug binding reduces sodium current. One obvious possibility is that drug binding at S6 (which lines the sodium permeation pathway) directs blocks current flow through the channel pore. Another likely mechanism is that drug binding alters the transitions channels undergo among rest, open, and inactivated states: support for this allosteric block concept comes from experiments in which inactivation is removed by site directed mutagenesis in the III–IV linker, and drug block thereby inhibited.[31]

Mutant channels may display altered drug sensitivity

With the increasing catalog of disease-related *SCN5A* mutations has come the recognition that some of these mutant channels display unusual drug sensitivity. For example, D1790G and Y1795H channels, both located in domain IV S6, display greater sensitivity to flecainide than wild type channels;[32] it is reasonable to think that mutations in this region may alter

access of the drug to a binding site. Another example is the N406S mutation located in domain I S6.[33] The index patient failed to show an expected response to challenge with a sodium channel blocking agent (pilsicainide, a class Ic drug) and the authors postulated that this reflected an absence of use-dependent block by the drug, attributable to the mutation. Interestingly, the N406S channel displayed greater than expected use-dependent block by quinidine, which could reflect differences in the physicochemical properties of the two antiarrhythmics.

Another interesting example of the way in which molecular genetics has informed drug therapy is the observation that Brugada syndrome mutations producing their clinical effects by reducing cell surface expression of mutant channels can be “rescued” by the administration of blocking drugs.[34, 35] Non-sodium channel blocking drugs have also produced this effect; for example, the potent I_{Kr} blocker cisapride increased cell surface expression of the L1825P mutant.[36] The usual explanation for this finding is that drug block to the mutant channel stabilizes it in a conformation that is not recognized as misfolded and therefore allowed to traffic to the cell surface.[37] While mistrafficking can be rescued *in vitro*, translation to clinical utility is more problematic not only because blocking drugs will certainly inhibit current once channels are expressed at the cell surface, but also because many mutant *SCN5A* channels display a mixed Long QT and Brugada syndrome phenotype: “rescuing” the Brugada phenotype would then run the risk of exacerbating the long QT phenotype, as was suggested in the initial cisapride report,[38] and others.[39]

IN VIVO MECHANISMS OF SODIUM CHANNEL BLOCKING DRUG ACTION

Sodium channel blockers can suppress arrhythmia arising through either abnormal automaticity or reentry. Reentry due to an anatomic or functional substrate is critically dependent on heterogeneous electrophysiologic properties, and slow conduction specifically enables reentry. Fast conduction in atrium, ventricle, and Purkinje is critically dependent on expression of sodium channels at the ends (intercalated disks) of cardiomyocytes. Thus, a widely held view is that if sodium channel blocking drugs interrupt reentry, they do so by further depressing conduction, and thus converting unidirectional to bidirectional block. An exclusive focus on conduction, however, leads to the conclusion that sodium channel block should almost inevitably be proarrhythmic in reentry. This view is supported by clinical observations such as CAST and before, and subsequent studies in animal models of myocardial infarction that showed that drugs such as flecainide can enable reentry by slowing conduction sufficiently to allow ventricular tachycardia to establish itself.[40] A more complex example of proarrhythmia due to conduction slowing by sodium channel blockers (usually class Ic agents but also seen with quinidine and with amiodarone) can occur in atrial flutter. Here, drug-induced conduction slowing in the flutter circuit paradoxically enables 1:1 atrioventricular (AV) conduction with an increase in ventricular rate. The use-dependent properties of the culprit drugs then widen the QRS duration so the resultant clinical arrhythmia resembles ventricular tachycardia.[41] For this reason, when these drugs are prescribed in patients with atrial fibrillation or flutter, AV nodal blocking drugs such as beta-blockers are frequently co-prescribed.

However, drug block will also persist during and after the action potential, and thereby prolong refractoriness, and it may be that it is this effect that is antiarrhythmic.[42] A further wrinkle has been the ability to model the effect of sodium channel block in unstable reentry caused by rotors or multiple wavelets. In this situation, sodium channel block may decrease vulnerability to initiation of fibrillation and, by modulating conduction from the mother rotor, lead to instability of the fibrillatory activity and thereby termination.[43] Other studies have suggested that sodium channel block can terminate reentry by enlarging the inexcitable center of a rotor, decreasing anchoring (and thereby increasing meander and extinction), and/or by reducing the number of daughter wavelets.[44]

Proarrhythmia in the structurally normal heart

The recognition that loss of sodium channel function in Brugada syndrome predisposes to ventricular fibrillation even in the structurally normal or near-normal heart, and that this can be exacerbated by administration of sodium channel blocking drugs, indicates that structural heart disease is not a *sine qua non* for sodium channel blocking drug proarrhythmia. An *SCN5A* promoter variant common in Asians appears to reduce channel expression, and increase both baseline QRS duration and the extent to which class Ic challenge further prolongs QRS.[45] These data suggest the hypothesis that variants, in *SCN5A* regulatory regions or in genes controlling *SCN5A* expression,[46, 47] may reduce sodium channel density and predispose to proarrhythmia. This is an appealing scenario in settings such as CAST, or the occasional development of a Brugada Syndrome ECG pattern in a patient treated with flecainide for atrial fibrillation, but further work is required to identify such polymorphisms and their potential role in mediating variable drug responses.

Another situation in which sodium channel block even in the normal heart appears to contribute to cardiovascular morbidity and mortality is tricyclic antidepressant overdose. These drugs, notably imipramine and nortriptyline, have been associated with an increased risk of SCD and in overdose typically produce wide complex rhythms which are either ventricular tachycardia or drug-induced sinus tachycardia with use dependent conduction slowing, resulting in wide QRS complexes.[48] Data from human and experimental annals have suggested that increasing extracellular sodium (by sodium bicarbonate or even sodium chloride administration) can shorten QRS duration and potentially exert antiarrhythmic effects.[49–52]

Another intervention that has proven useful in cases of class Ic-related proarrhythmia is administration of beta-blockers. One likely mechanism is that by slowing sinus rate, beta-blockers decrease the extent of use-dependent block and therefore reduce proarrhythmia.[53] The idea that sodium channel block can confer proarrhythmic effects has generated interest in the regulatory community in the relationship among sodium current blocking potency and QRS prolongation as a function of plasma concentration of drugs. One report suggested that drugs for which the maximum expected plasma concentration was at least thirtyfold lower than the concentration required to block 50% of sodium current was an acceptable safety margin.[54] However, the blocking potency of drug as a function of voltage or rate was not explicitly considered. Further, animal studies have indicated that the relationship between sodium current recorded in a cardiomyocyte and fast conduction may be dissociated with

specific mutations in the channel itself[55] or altered function of proteins such as dystrophin and SAP97 that guide its delivery to specific subdomains in the cell.[56]

Most sodium channel blockers exert other pharmacologic effects

Almost all sodium channel blocking drugs, with the probable exception of lidocaine and mexiletine, exert prominent effects on other pharmacologic targets, notably ion channels, and these effects, in turn, complicate interpretation the extent to which sodium channel block contributes to clinical effects observed.

Quinidine, for example, is a very potent blocker of I_{Kr} and a modestly potent blocker of the transient outward current I_{to}, and these effects likely contribute to its clinical actions. In particular, quinidine even at low doses can frequently produce torsades de pointes, and this likely reflects its I_{Kr} blocking action.[57, 58] The effect of quinidine to block I_{to} has been proposed as an antiarrhythmic effect ("balancing" the loss of sodium current) in Brugada syndrome and this has been demonstrated in both tissue preparations[59] as well as in occasional patients, especially those with VT storm in whom quinidine appears effective.[60, 61]

Another example is the unexpected efficacy of flecainide in suppressing arrhythmias and catecholaminergic polymorphic ventricular tachycardia (CPVT). CPVT is caused by "leaky" RYR2 channels, and the initial demonstration of flecainide efficacy in a mouse model of CPVT led to identification of its RYR2-blocking properties and demonstrations of clinical efficacy.[62, 63] These are shared with propafenone (and notably the R-enantiomer) but not with other sodium channel blocking agents, and propafenone and flecainide appear unusually effective in CPVT compared to other sodium channel blockers.[64]

Other reports have demonstrated that propafenone is a relative blocker of cardiac two pore domain potassium channels,[65] and that the beta blocker propranolol may exert antiarrhythmic effects in certain forms of the long QT syndrome by blocking sodium channels, albeit at relatively high concentrations.[66]

The late sodium current

The macroscopic signature of sodium current during a voltage clamp experiment is rapid activation followed by rapid inactivation back to baseline. Experiments in the 1970s demonstrated that in some tissues (initially the node of Ranvier[67]), fast sodium channel inactivation might be incomplete and therefore a persistent current could develop during long voltage clamp steps could develop; subsequent studies showed that a low concentration of TTX could shorten action potentials in dog Purkinje fibers without affecting maximal phase 0 upstroke slope, supporting the idea of an inward sodium current flowing during the action potential plateau.[68] A body of evidence now supports the view that inhibition of this persistent or late sodium current ($I_{Na\text{-}L}$) can suppress arrhythmias without significant proarrhythmic potential.

Two mechanisms underlying $I_{Na\text{-}L}$ have been described, and both are probably operative in some clinical situations. One is a "window" mechanism reflecting overlap of the voltage dependence of steady state activation and inactivation such that at overlap voltages

activation and inactivation are non-zero.[68] A second mechanism is a "bursting behavior"[69] reflecting instability of the fast inactivation mechanism. The latter is now most commonly associated with type 3 (*SCN5A*-linked) congenital long QT syndrome mutations (the first one described involves the fast inactivation "particle" in the domain III–IV linker)[70] but is also recognized in normal tissues, notably those with long action potentials such as the Purkinje cells and the mid-myocardial (M cell) layer.[71]

The mechanism whereby certain tissues display $I_{Na\text{-}L}$ while others do not has not been fully worked out. One possibility is raised by the observation that activation of calmodulin kinase II increases $I_{Na\text{-}L}$,72 suggesting that variable activation of this or other signaling pathways underlies the presence or absence of late sodium current in specific cells. Another candidate pathway is suggested by the observation that hours of exposure to some QT prolonging drugs can inhibit PI3 kinase, and this in turn increases $I_{Na\text{-}L}$.73 The current is blocked not only by TTX, but also by sodium channel blocking drugs such as flecainide[74] or mexiletine,[75] and these drugs have been used in LQT3, although they may also provoke the Brugada ECG in this setting.[76]

In addition, $I_{Na\text{-}L}$ block is the likely major mechanism of antiarrhythmic action of the anti-anginal agent ranolazine.[77] The drug appears modestly selective for late sodium current versus peak sodium current,[78] and also blocks I_{Kr} at somewhat higher concentrations than those required to block late sodium current; the clinical effect is to prolong QT interval minimally, if at all, presumably due to late sodium current block. Ranolazine has not been associated with torsades de pointes during clinical use and in animal models the drug's late sodium channel blocking properties appear to inhibit experimental long QT related arrhythmias.[79] In a large clinical trial in patients with coronary disease, the drug produced no evidence of CAST-like (or other) proarrhythmia.[80] Ranolazine is currently being evaluated as a potential antiarrhythmic in other settings, including atrial fibrillation,[81] and other more selective late cardiac sodium current blockers have been developed.[82, 83]

SUMMARY

Sodium channel blocking drugs carry proarrhythmic potential. This was recognized with the use of high dose quinidine in the first half of the 20th century, with the use of encainide and flecainide in patients with advanced heart disease in the 1980s, in CAST, in atrial flutter, and with the recognition sodium channel block exacerbates the electrocardiographic and arrhythmia susceptibility phenotype in the Brugada syndrome. Despite this risk, the drugs continue to be used, notably in the treatment of atrial fibrillation with the caveat that they should be avoided in patients with structural heart disease or in patients in whom the Brugada electrocardiogram is present or emerges during treatment.

Modeling studies have suggested that drugs with appropriate combinations of potassium channel inhibition and specific frequency and/or voltage dependent sodium channel block could be antiarrhythmic with minimal proarrhythmic potential. One such study suggested that drugs targeting inactivated channels could be atrial fibrillation-selective.[84] The newer agent AZD1305 is highly effective in animal models of atrial fibrillation and appears to induce far greater sodium channel block in atria than in ventricles;[85] this effect is also seen

with ranolazine and may reflect differences between atrial and ventricular tissue in the voltage-dependence of fast inactivation.[86] It is also possible that with a deeper understanding of the structure function of the cardiac sodium channel will come opportunities to target entirely new regions of the channel or its function-modifying protein partners to modulate its activity to suppress arrhythmias without proarrhythmia.

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KEY POINTS

- Sodium channel blocking drugs carry proarrhythmic potential; despite this risk, however, the drugs continue to be used, notably in the treatment of atrial fibrillation with the caveat that they should be avoided in patients with structural heart disease or in patients in whom the Brugada electrocardiogram is present or emerges during treatment.
- Modeling studies have suggested that drugs with appropriate combinations of potassium channel inhibition and specific frequency and/or voltage dependent sodium channel block could be antiarrhythmic with minimal proarrhythmic potential.
- The newer agent AZD1305 is highly effective in animal models of atrial fibrillation and appears to induce far greater sodium channel block in atria than in ventricles; this effect is also seen with ranolazine and may reflect differences between atrial and ventricular tissue in the voltage-dependence of fast inactivation.
- It is possible that with a deeper understanding of the structure function of the cardiac sodium channel will come opportunities to target entirely new regions of the channel or its function-modifying protein partners to modulate its activity to suppress arrhythmias without proarrhythmia.