



# Trails of Discovery

## *Class III antiarrhythmic agents: serendipity or drug design?*

**J. Desmond Fitzgerald, BSc, FRCP, FFPM**

*Materia Medica - Mere, Knutsford - UK*

The classification of antiarrhythmic drugs proposed by Singh and Vaughan Williams in 1970<sup>1,2</sup> relied on the differential actions of these agents on the profile of the transmembrane action potential in isolated myocardial tissue from different species. Despite the dramatic advances over the last 15 years in understanding the molecular and ionic basis, which determine the profile of the transmembrane action potential, the original classification persists in both the clinical and government regulatory spheres. The field of Class III antiarrhythmic drug research has been illuminated by numerous publications in a most fruitful manner over the last 30 years by Professor Braham Singh, who provides an elegant example of what is now translational medicine, ie, applying data from the laboratory to the bedside. This essay is largely based on Professor Singh's seminal work.<sup>3-7</sup>

### **FIRST-GENERATION CLASS III AGENTS: AMIODARONE AND SOTALOL**

Amiodarone and sotalol provide striking examples of the role of serendipity in drug discovery. Amiodarone was initially developed as a selective coronary

vasodilator for the treatment of angina pectoris, and sotalol was a nonselective  $\beta$ -blocker first synthesized at the same time as the classic  $\beta$ -blockers pronethalol and propranolol (1959-1962).

### **DISCOVERY OF AMIODARONE**

Amiodarone was one of a large number of benzofuran analogs synthesized in the Labaz Laboratories in Belgium between 1958-1966.<sup>8,9</sup> The rationale for the synthetic program was based on the natural product, khellin, which was used in the Middle East as a diuretic and antispasmodic. Khellin was isolated from the seeds of the plant *Ammi visnaga*, called in Arabic "khella." The first paper from the Labaz Laboratories describes the coronary vasodilator properties of a series of benzofurans derived from the furanochromone structure of khellin.<sup>9</sup> In regard to the rationale for the research program, the paper quotes the work of Anrep et al<sup>10</sup> published in 1945, which concluded that khellin (120 mg daily) was effective in 36 of 38 anginal patients. The Labaz paper also notes that Greiner et al<sup>11</sup> had failed to confirm Anrep's observations. Nevertheless, the Labaz scientists appear to have concluded that the proof of concept of the antianginal action of khellin was established. Furthermore, the khellin preparation was marketed by Smith-Kline in the early 1950s and is still classified in the Martindale *Extra Pharmacopoeia* under Supplementary Drugs and Other Substances.<sup>12</sup>

Eighty-one benzofurane analogs were synthesized and tested in vitro for their antispasmodic activity on smooth muscle as well as their coronary dilating action in the isolated, fibrillating, rabbit heart. In these in vitro tests, khellin was used as the benchmark coronary vasodilator.<sup>9</sup> Compound L2329 (Amplivix®, benziodarone) was developed for clinical studies in angina pectoris.<sup>13,14</sup>

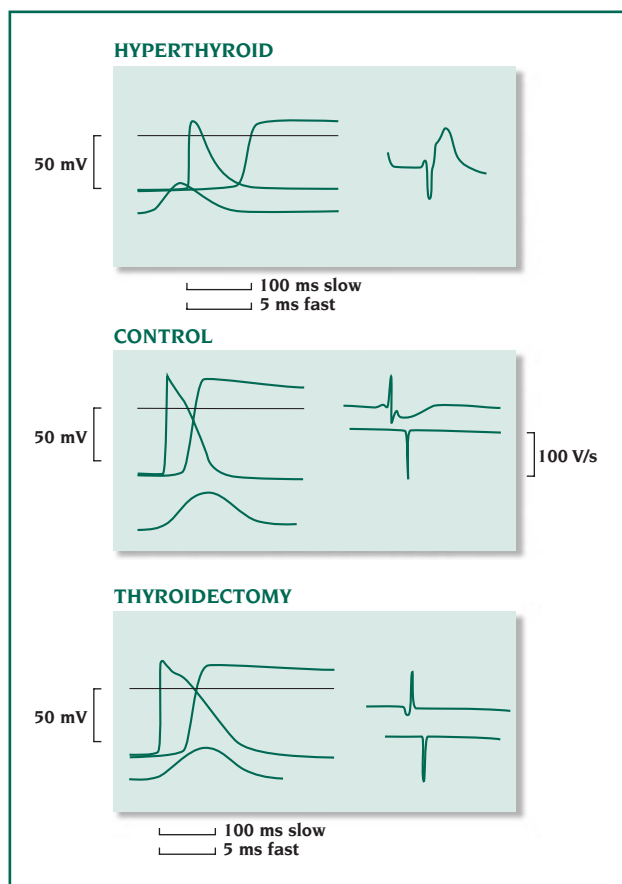
Clinical trials in the early 1960s showed that it was effective in reducing the number of anginal attacks and increasing exercise tolerance. It was also observed that it slowed the heart rate. A paper from the Labaz Laboratories in 1969<sup>15</sup> states that a clinical investigator had observed that amiodarone had antiarrhythmic properties. The published paper<sup>14</sup> does not refer to a reduction of arrhythmias, but only of heart rate in anginal patients treated with amiodarone 600 mg daily for a month. Interestingly, the paper reports that "the depolarization complex of the ECG showed no change." The introduction to the paper by Charlier et al<sup>15</sup> refers to "a chance observation of normalization of cardiac rhythm in an anesthetized dog following amiodarone 10 mg/kg/ IV," although the paper they quote contains only clinical studies in anginal patients.

Nevertheless, the Labaz scientists re-evaluated amiodarone in several experimental arrhythmia models and attributed their positive findings to a combination of the sympatholytic and quinidine-like actions of amiodarone.<sup>15</sup>

#### **Address for correspondence:**

Dr J. Desmond Fitzgerald, Materia Medica, Mere Croft, Chester Road, Mere, Knutsford, Cheshire WA16 6LG, UK  
(e-mail: des.fitzgerald@tiscali.co.uk)

*Dialogues Cardiovasc Med.* 2004;9:243-252



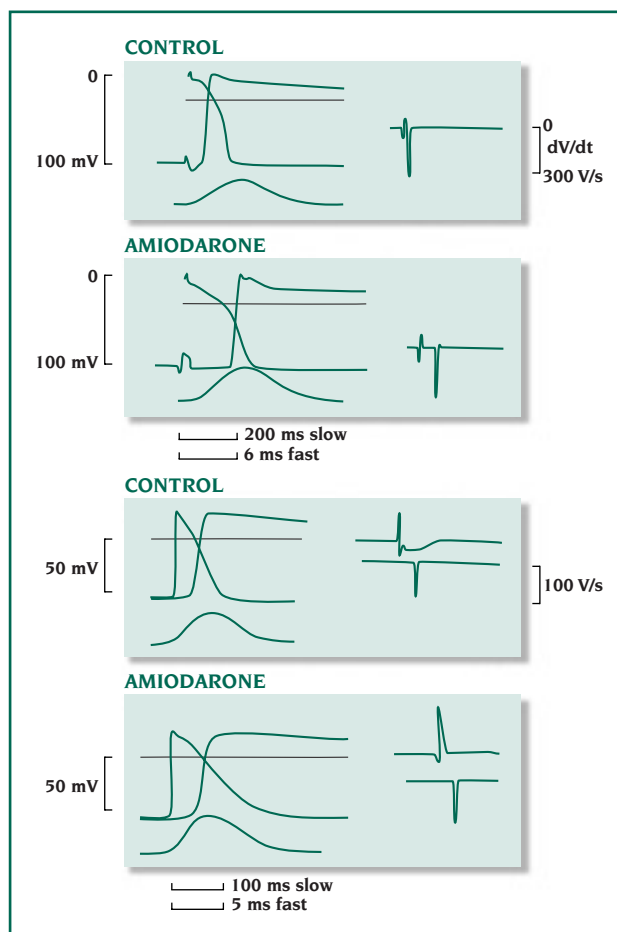
**Figure 1a.** The effect of thyroid state on cardiac intracellular potentials. The horizontal line in each frame indicates the zero potential and the superimposed traces record intracellular action potentials at both slow and fast sweep speeds. The lowest trace records the contractile response.

From reference 16: Freedberg AS, Papp J, Vaughan Williams EM. The effect of altered thyroid state on atrial intracellular potentials. *J Physiol Lond.* 1970;207:357-370. Copyright © 1970, Blackwell Publishing.

During this same period, Vaughan Williams' group in Oxford published a series of papers examining the effects of different drugs on the myocardial transmembrane action potential. These studies resulted in a proposal to classify antiarrhythmic drugs into at least three categories.<sup>2</sup> His group had also observed the effects of experimental hypothyroidism on the transmembrane action potential in rabbits and showed that six weeks after thyroidectomy the action potential duration was significantly prolonged (*Figure 1a*).<sup>16</sup>

Dr Bramah Singh, who was a Commonwealth Fellow born in Fiji and trained in medicine in Otago University, New

Zealand, joined Professor Vaughan Williams group in the late 1960s in order to do a PhD degree. The topic chosen was "The study of the pharmacological actions of certain drugs and hormones with a particular reference to cardiac muscle." Included in this research program was an evaluation of the effects of chronic amiodarone treatment on the transmembrane action potential after chronic administration (20 mg/kg IP) to rabbits. He showed that amiodarone specifically prolonged the action potential duration (APD) without significant effects on the resting potential or the rate of rise of the action potential (*Figure 1b*). The precise rationale for selecting amiodarone



**Figure 1b.** The effects of 6 weeks treatment with amiodarone (20 mg/kg/IP daily) in rabbit atrial muscle, above, and in ventricular muscle, below.

From reference 3: Singh BN, Vaughan Williams EM. The effects of amiodarone, a new anti-anginal drug, on cardiac muscle. *Br J Pharmacol.* 1970;39:657-667. Copyright © 1970, Nature Publishing Group.

for study is not stated in the published papers or the thesis. One may speculate that it was the di-iodo substitution in amiodarone that was the stimulus for its selection, though it was claimed at the time to have no effect on thyroid function. In addition, amiodarone had complex effects on the autonomic system, causing an atropine-resistant bradycardia in dogs and inhibition of sympathetic nerve stimulation and catecholamines, but not due to specific blockade of  $\alpha$  or  $\beta$  adrenoceptors.<sup>17</sup>

This combination of pharmacological attributes made it an interesting tool for exploring the mode of action of antiarrhythmic compounds.



Site of ADR	Number of trials reporting	Number affected in amiodarone group	Number affected in placebo group	Peto odds ratio (25% CI)	P-value
Heart	6	98/2087	43/2066	2.40 (1.69, 3.41)	<0.00001
Thyroid	5	74/2038	12/2014	4.19 (2.72, 6.45)	<0.00001
Respiratory	6	76/2087	42/2066	1.78 (1.23, 2.58)	0.002
Nervous system	5	48/1782	19/1758	2.40 (1.48, 3.89)	0.0004
Liver	5	30/1782	14/1758	1.95 (1.07, 3.56)	0.03
Gastrointestinal tract	5	66/2038	47/2014	1.32 (0.9, 1.94)	0.15
Eyes	4	23/1702	6/1676	3.05 (1.46, 6.38)	0.003
Skin	6	24/2087	12/2066	1.93 (1.00, 3.72)	0.05

**Table I.** Meta-analysis of adverse effects of amiodarone in six randomized controlled trials.

*Modified from reference 20: Loke YK, Derrey S, Aronson JK. A comparison of three different sources of data in assessing the frequencies of adverse reactions to amiodarone. Br J Clin Pharmacol. 2004;57:616-621. Copyright © 2004, Blackwell Publishing.*

## CLINICAL STUDIES

The major clinical utility of amiodarone is in the prophylactic control of supra-ventricular and ventricular arrhythmias. Parenteral amiodarone (5 mg/kg by slow injection) slows the ventricular response in atrial flutter and fibrillation. Observational studies suggest that it is also effective acutely in the control of life-threatening ventricular arrhythmias.<sup>18</sup> Its major utility is as chronic therapy (200-400 mg daily), firstly to control the ventricular response in atrial flutter and fibrillation both at rest and on exercise. Secondly, amiodarone has had a major impact on the treatment of recurrent life-threatening ventricular tachyarrhythmias. It is currently the drug of choice for this indication. Remarkably, it has much less proarrhythmic activity than many other antiarrhythmic drugs.<sup>19</sup> The most serious unwanted effect is pulmonary toxicity, which occurs in 2% to 17% of patients and is observed with doses higher than 300 mg daily. Between 2% and 10% of patients receiving amiodarone have alterations in thyroid function, and given the arrhythmogenic potential of thyrotoxicosis, can reverse the antiarrhythmic effects of chronic amiodarone therapy (Table I).<sup>20</sup>

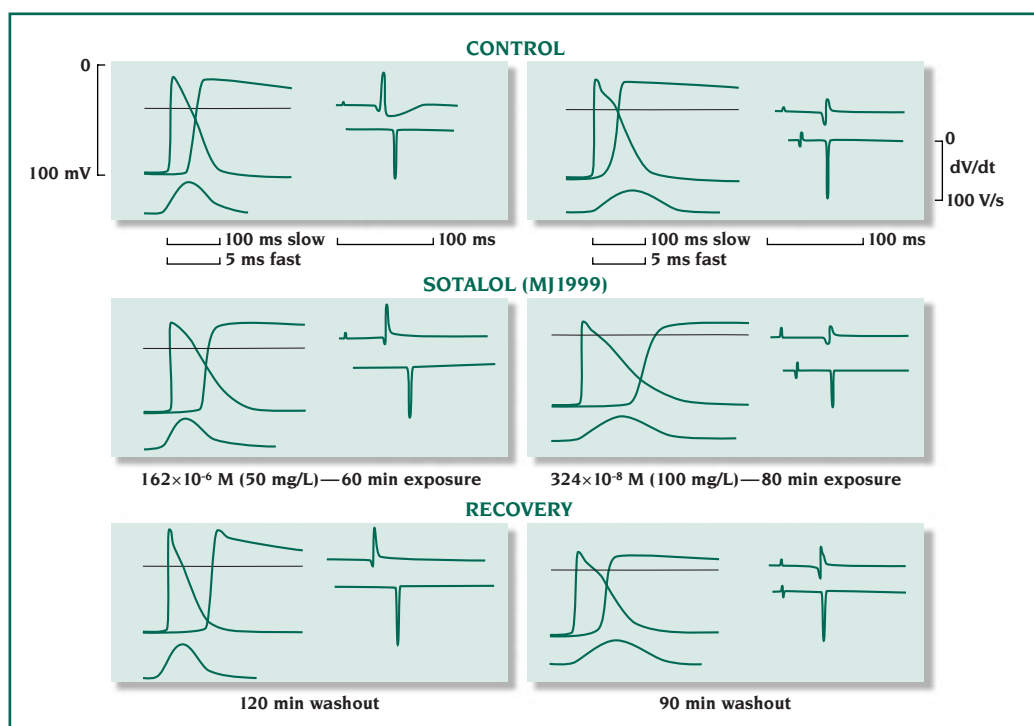
## THE DISCOVERY OF SOTALOL

This compound was synthesized in about 1960 by the Mead Johnson Company, in Indiana, USA.<sup>21</sup> It was one of a series of analogs submitted to the US Patent Office in January 1962, the patent was subsequently abandoned and then refiled and finally completed in 1965. The patent made broad claims including "vasopressors, vasodepressors, analgesics, bronchodilators,  $\alpha$ -receptor stimulants,  $\beta$ -receptor stimulants,  $\alpha$ -receptor blocking agents,  $\beta$ -receptor blocking agents, and papaverine-like smooth muscle depressants." DL-Sotalol was compound No. 11 in this patent, but the preferred compound was No. 3, possessing "strong and selective adrenergic vasoconstrictor emphasized activity." Thus the  $\beta$ -blocking properties of sotalol (Compound 11) are not described in the initial patent.<sup>22</sup> Ironically, sotalol would have been synthesized at the same time as pronethalol and propranolol in the ICI laboratories by Crowther and Black (1958-1964), but sotalol's potential therapeutic utility was not initially recognized, although eventually extensive clinical studies were undertaken.<sup>23</sup> It was shown that sotalol had a more attractive pharmacokinetic and phar-

macodynamic profile than propranolol. Unlike propranolol, it was not extensively metabolized and 80% was excreted unchanged in the urine while having a half-life of about 10 hours compared with propranolol's half-life of 2 hours. In addition, it had much less brain penetration. Perhaps more importantly, it did not have significant "membrane-stabilizing properties" or quinidine-like actions and had much less direct myocardial depressant properties.

The unique property of sotalol in prolonging action potential duration in cat papillary muscle was first published by Kaumann and Olson in 1968.<sup>24</sup> They showed that sotalol (MJ1999) in a concentration of  $6 \times 10^{-4}$  M lengthened APD from  $401.3 \pm 46.4$  ms (control) to  $1209.4 \pm 290$  ms at 90% repolarization. In the conclusion of their paper, they attribute its antifibrillatory properties in experimental canine infarction<sup>25</sup> to the fact that "It appears that the antifibrillatory activity of sotalol, unlike that of other presently-known antiarrhythmic agents, is attributable to the marked prolongation of the ventricular action potential."

In 1970, Singh and Vaughan Williams published their findings on the effects of MJ1999 on the transmembrane ac-



**Figure 1c.** The effect of sotalol (MJ1999) on intracellularly recorded potentials of rabbit atria.

From reference 2:  
Vaughan Williams EM. Classification of antiarrhythmic drugs. In: Sandoe E, Flensted-Jensen E, Olesen KH, eds. Symposium on Cardiac Arrhythmias. Sodertalje, Sweden: AB Astra; 1970: 449-469. Copyright © 1970, Astra. All rights reserved.

tion potential in isolated ventricular and atrial muscle and confirmed that it greatly prolonged the duration of the action potential (Figure 1c).<sup>17</sup> In their discussion, they also made the point that “the main interest of the delay in repolarization produced by MJ1999 is that it is an immediate effect, apparent after a few minutes exposure to the drug in vitro, whereas the effect produced by thyroidectomy and amiodarone takes several weeks to develop.”<sup>1</sup> Several years later it was shown that sotalol prolonged the monophasic action potential duration in man, as well as an acute increase in effective refractory period.

In an elegant study, Creamer et al compared the effects of acute and chronic administration of sotalol with those of propranolol in patients with programmable pacemakers. Sotalol prolonged the QT interval by 11.5% after 1 month's oral treatment, with a lesser effect of 6.5% following acute parenteral administration. Propranolol did not cause any change in the QT interval.<sup>27</sup> Extensive clinical studies with DL-so-

talol showed that it is effective in controlling both supraventricular and ventricular arrhythmias. The balance of evidence suggested that the dual effects of  $\beta$ -blockade (Class II) and prolongation of APD (Class III) gave the best clinical results.<sup>28</sup> This may be important for the prevention of sudden death in postinfarction patients, where the Class III agent D-sotalol was shown to be less effective than placebo.<sup>29</sup> It is not the purpose of this article to review the comparative effectiveness of different classes of antiarrhythmic drugs, but rather to describe the subsequent impact on cardiovascular research strategies within the pharmaceutical industry of the initial discovery of the selective specific prolongation of action potential duration (Class III drugs).

#### SUBSEQUENT DEVELOPMENTS IN CLASS III DRUG RESEARCH

The potential therapeutic utility of selective prolongation of APD was widely recognized.<sup>30</sup> The perceived disadvan-

tages of amiodarone included poor bioavailability, complex pharmacological profile, and unacceptable side effects. Thus, research was directed toward finding patentable, potent, highly selective Class III compounds. There were two assumptions underlying this strategy. Firstly, the beneficial antiarrhythmic effects of amiodarone were attributed almost entirely to its Class III properties and secondly, high specificity for the major ion channel involved in APD prolongation, namely,  $I_{Kr}$ , enabled in vitro testing to proceed rapidly.

The research strategy was highly successful, in that at least 18 pharmaceutical companies initiated research programs designed to discover improved Class III antiarrhythmic agents (Figures 2a and 2b, page 247 and 248). Such programs would be dominated by medical chemistry conceptual skills, using one or more of the four original Class III chemical templates, namely, sotalol, isopropyl nitrophenylethanolamine (INPEA), *N*-acetyl procainamide (a metabolite of procaine with selective Class III actions), and



amiodarone. The majority of research groups synthesized chemical series in which the methanesulfonamidophenyl group, present in sotalol, was retained (Figure 2b). For example, this substitution in a structure based on *N*-acetyl procainamide (NAPA) resulted in the development of sematilide (Berlex). Similarly, Pfizer chemists prepared a large chemical series based on the sotalol structure, resulting in 21 published patents and the development

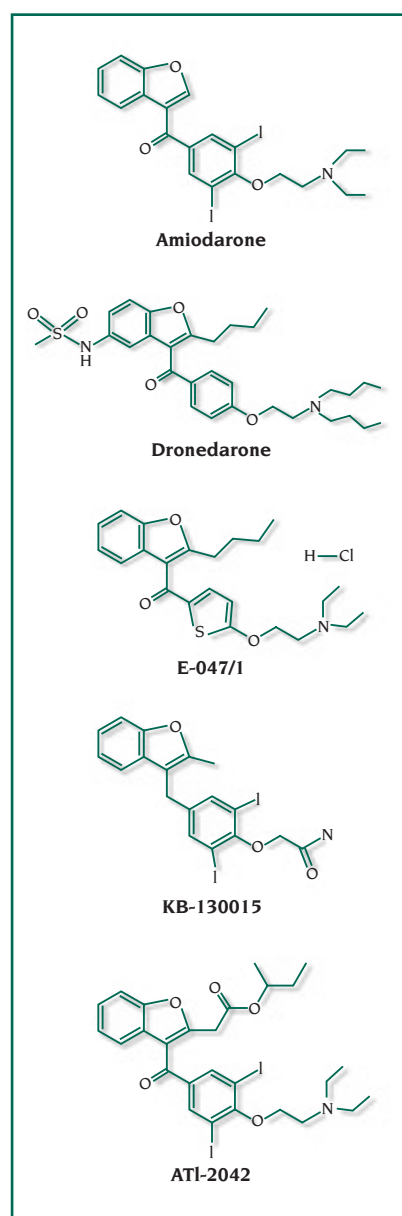


Figure 2a. Chemical structures of amiodarone and benzofuran analogs.

Drug	Cardiac channel	Dose range (mg)	T <sub>1/2</sub> (h)	Excretion
Dofetilide	$I_{Kr}$	0.125-0.5 PO bid	8	Kidney ≈80%
Sematilide	$I_{Kr}$	100-150 PO tid	3-8	Kidney ≈75%
Ibutilide	$I_{Kr}$ slow Na current	0.5-2 IV	6	Liver
Azimilide	$I_{Kr}$ $I_{Ksr}$ $I_{Ca(L)}$	100-125 PO od	100-120	Liver
Dronedarone	$I_{Kr}$ $I_{to}$ $I_{K(Ach)}$ $I_{Ks}$ $I_{Ca(L)}$	400 PO bid	150	Liver
Tedisamil	$I_{to}$ $I_{Kr}$	100 PO bid	16	Kidney

Table II. Cardiac and pharmacokinetic properties of newer "Class III" drugs.

of dofetilide (UK68798). The overall result of this intense drug research activity is somewhat limited in proportion to the enormous investment (Table II).

At present, the only Class III antiarrhythmic drugs approved for parenteral and oral use are dofetilide (Pfizer), indicated for the conversion (parenteral) or maintenance (oral) of sinus rhythm in patients with atrial fibrillation. As dofetilide also causes QT prolongation and, in some instances, torsades de pointes, treatment should be initiated in hospital, titrating the dose in relation to both the QT interval and the status of renal function.<sup>31</sup>

The other Class III compound is ibutilide, approved only for parenteral use for acute chemical conversion of atrial fibrillation or atrial flutter, as a possible alternative to DC cardioversion. In addition to blocking the  $I_{Kr}$  channel, it activates a sustained sodium channel, which must be distinguished from the "fast" sodium channel.<sup>32</sup>

There are three other Class III agents in phase 3 clinical trials: tedesamil, azimilide, and dronedarone, none of which block solely the  $I_{Kr}$  channel.

At this point, it is perhaps worth reflecting how advances in the understanding of the molecular mechanisms underlying the genesis of the cardiac action potential have influenced the approach to devising improved antiarrhythmic agents. In the context of

prolonging APD in order to prolong the refractory period, at least seven potassium channels may play a role (Table III, page 249).<sup>33</sup> A further difficulty for "pure"  $I_{Kr}$  blockers is that the prolongation of APD induced by them is reduced at rapid heart rates, a clinical situation that often requires efficacy in antiarrhythmic therapy at high heart rates. This phenomenon is termed "reverse use dependence."<sup>34</sup>

An additional disadvantage of their greater blocking efficacy at slow heart rates is that excess APD prolongation may trigger early afterdepolarizations, possibly leading to torsades de pointes. It is now apparent that the voltage-gated "delayed rectifier" potassium current ( $I_K$ ) is composed of two different currents carried by different ion channel species, namely, the "slow" component  $I_{Ks}$  comprising a major subunit (KCNQ1) and a minor unit (KCNE1). The rapid component ( $I_{Kr}$ ) is composed of the HERG (human ether-a-go-go-related gene) protein as the major subunit and KCNE2 as the accessory subunit. At high heart rates (high depolarization frequencies), the  $I_{Ks}$  outward current becomes the major one and selective blockade of  $I_{Kr}$  has little effect on APD in this setting. The chronic administration of amiodarone significantly decreases both  $I_{Kr}$  and  $I_{Ks}$  so that the APD prolongation does not show reverse use dependence. The lower incidence of torsades de pointes on amiodarone therapy has been attributed to this dual action.

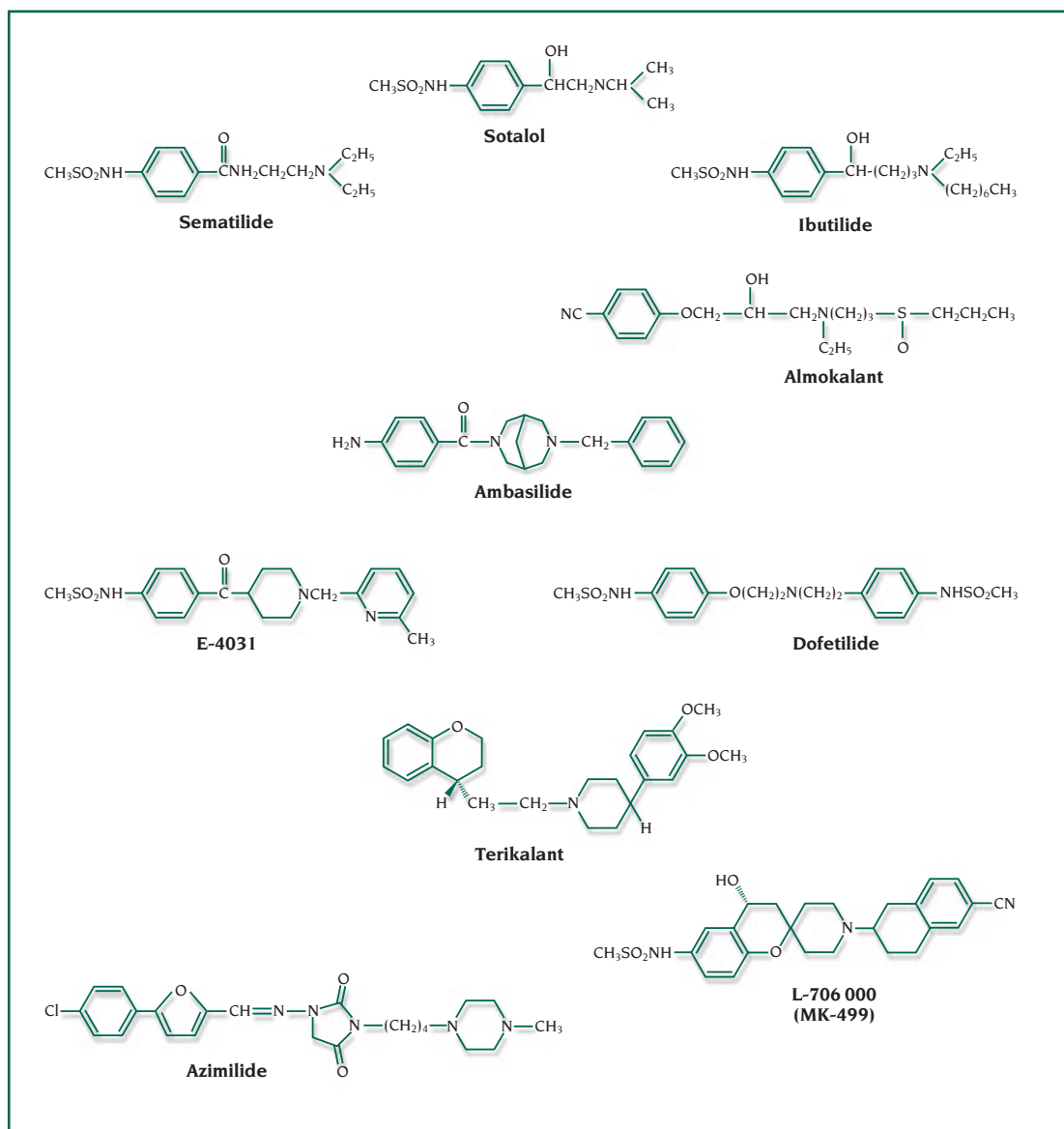


Figure 2b. Chemical structures of Class III agents based on the sotalol template.

It is perhaps ironical that potent binding to the HERG protein in the  $I_{Kr}$  channel is now perceived as a disadvantageous property of Class III agents because of proarrhythmia potential. Regulatory agencies now require data on the effects of any novel compound on the HERG channel prior to human exposure. In retrospect, perhaps drug researchers seeking an improved amiodarone were somewhat misled by assuming that its major desirable property was prolongation of APD solely by selective  $I_{Kr}$  blockade.

### THE SEARCH FOR AN IMPROVED AMIODARONE

The cardiac channel actions of amiodarone include potent inhibition of the  $K_r/K_s$  channels, moderate inhibition of the cardiac  $\alpha$  and  $\beta$  receptors, as well as of the  $L\text{-}C_a$  channel and the fast sodium channel. The challenge in seeking an improvement on amiodarone is to decide how many of these properties contribute to its antiarrhythmic efficacy. Amiodarone is more efficacious than all other antiarrhythmic

drugs in treating atrial fibrillation, and is better than placebo or lidocaine for treating ventricular fibrillation. The electrophysiological properties of acutely administered amiodarone are markedly different from those observed following chronic oral therapy, which results in APD prolongation. It is noteworthy that the original studies by Singh involved the study the effects of long-term intraperitoneal administration to rabbits for prolonged periods followed by ex vivo studies on the atria and ventricles. A single parenteral dose of



Channel name	Abbreviation	Gene	A-subunits	Selective blocker
Rapid delayed rectifier	$I_{Kr}$	<i>KCNH2</i>	ERG1	Class III (agents)
Slow delayed rectifier	$I_{Ks}$	<i>KCMQ1</i>	$K_V$ LQT (Mink)	Class III (agents)
Inward rectifier	$I_{K1}$	<i>KCMJ4</i>	$K_{IR}$ 2.3	Tertiapin (venom)
ATP-gated channel	$I_{K-ATP}$	<i>KCNJ8</i> <i>KCNJ11</i>	$K_{IR}$ 6.1/6.2	↑ ATP
Muscarinic	$I_{K-Ach}$	<i>KCNJ3</i> <i>KCNJ5</i>	$K_{IR}$ 3.1 $K_{IR}$ 3.4	Atropine
Transient outward current	$I_{tol}$	<i>KCND3</i> <i>JCNA4</i>	$K_V$ 2/4.2 $K_V$ 21.4	
Ultrarapid delayed rectifier	$I_{Kur}$	?	$K_V$ 1.5 (human) $K_V$ 1.3 (canine)	

**Table III.** Selected voltage-gated cardiac potassium ion channels.  $K^+$  channels consist of pore-forming ( $\alpha$ ) transmembrane subunits and accessory units that can markedly alter the properties of the channel.

amiodarone (5 mg/kg) causes only a significant lengthening of the AH interval and atrioventricular nodal effective refractory period, with no effect on the heart rate or the QTc interval. There is thus a marked disparity between the electrophysiological effects of acutely administered amiodarone and those observed after long-term treatment (Table IV).<sup>35</sup> The explanation for these differences is not clearly understood,

but possibly the interaction of amiodarone (and its major metabolite desethylamiodarone) with thyroid hormones may be important.<sup>36</sup> Amiodarone treatment causes a dose-dependent decrease in the expression of several  $T_3$ -dependent genes. The main metabolite, desethylamiodarone, inhibits the binding of  $T_3$  to its nuclear receptors. It is a competitive inhibitor at the  $\alpha_1$  thyroid hormone receptor

( $TR_{\alpha 1}$ ) and a noncompetitive inhibitor at the  $\beta_1$  thyroid hormone receptor ( $TR_{\beta 1}$ ). An additional complexity regarding the mode of action of amiodarone is that the contribution of the systemic and coronary vasodilator actions of amiodarone to its overall antiarrhythmic efficacy is not clearly established, though there is reason to believe that these effects are also beneficial.

The major shortcomings of amiodarone relate, firstly, to its suboptimal pharmacokinetics properties. It is variably absorbed from the gut and is widely distributed, accumulating in muscle and fat. It has an average half-life in humans of 50 days, ranging between 20 to 100 days. Its effects persist for up to 1 month after stopping therapy. Secondly, amiodarone treatment can be associated with a range of adverse effects involving multiple organ systems (Table II). These adverse events may be due in part to the iodine content of the molecule (ie, changes in thyroid status and ocular deposits), but the mechanism of the hepatic, skin, and pulmonary effects is not understood.<sup>20</sup>

Several research strategies have been adopted in seeking agents with an efficacy similar to amiodarone, but with better tolerability and pharmacokinetics. Close analogs of amiodarone have been made by one group, preserving both the benzofuran and di-iodo structures, but substituting ester homologs, in order to achieve better kinetics and more rapid onset of effect. The lead compound (ATI 2042) is in phase 2 clinical trials. It has a half-life in humans of 100 hours instead of the 50-day half-life of amiodarone. Experimental studies in isolated guinea pig hearts show that ATI 2042 increases atrial conduction time by 70% and APD and QTc by 10%.<sup>37</sup> It is not easy to understand the logic of this group's research strategy because of the widespread assumption that the iodo substitution in amiodarone, which is also present in ATI 2042, is a major contributor to its un-

Electrophysiological parameter	Acute	Chronic
Increase in: RR interval	±	+++*
PR interval	++	+++
QT/QTc	±	++++
AH interval	++	+++
QRS interval (rate-related)	++	+++
Atrial ERP	+	++++
AV nodal ERP	+++	++++
Ventricular ERP	±	++++
His-Purkinje ERP	±	+++
Bypass tracts (anterograde/retrograde)	±	++++

\* Sympatholytic action.

**Table IV.** Comparison of the electrophysiological effects of acute versus chronic amiodarone administration in man.

**Abbreviations:** AV, atrioventricular; ERP, effective refractory period.

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wanted side effects. The compound KBI 30015, produced by Karo Bio AB (Sweden), also retains the benzofuran and di-iodo substitutions, but the hypothesis is that amiodarone's action on chronic administration is mediated by inhibition of thyroid hormone action on the heart. KBI 30015 is an antagonist at both the human  $\alpha$  and  $\beta$  thyroid receptors ( $IC_{50}$  2.2 and 4.1 micro, respectively.<sup>7</sup> However, the electrophysiological effects in acute administration studies show that it reduces the cardiac sodium and  $I_{CaL}$  channels.<sup>38</sup> It seems unlikely that the acute effects are due to modification of thyroid hormone action on the heart.

An alternative strategy adopted by the scientists in the Sanofi laboratories had been to synthesize noniodinated analogs of amiodarone, preserving the benzofuran structure. The most advanced compound is dronedarone (SR 33589), which is in phase 3 clinical trials in atrial fibrillation.<sup>39</sup> The literature on the electrophysiological effects of dronedarone provides differing profiles, depending upon the animal species, whether the studies are in vitro or in vivo or are acute or chronic. Specifically, its effects in prolonging APD were not observed following acute administration to anesthetized dogs, but APD and QTc were significantly prolonged following chronic treatment ( $2 \times 20$  mg/kg/day) in a canine model of atrioventricular block.<sup>40</sup>

While the electrophysiological properties of dronedarone are not finally agreed upon, the dose-ranging trial in atrial fibrillation (postconversion) indicates that in a dose of 800 mg/day, it increased the time to recurrence of fibrillation from 5 days on placebo to 60 days on therapy.<sup>39</sup> Two additional phase 3 clinical trials are in progress (EURIDIS [EUROPEAN trial In atrial fibrillation or flutter patients receiving Dronedarone for the maintenance of Sinus rhythm] and ADONIS [American-Australian-African trial with Drone-

darONE In atrial fibrillation or flutter patients for the maintenance of Sinus rhythm), but the results are not currently available. A trial of its antiarrhythmic effects in moderate-to-severe chronic heart failure (ANDROMEDA [Antiarrhythmic trial with DRonedarone in Moderate to severe CHF Evaluating morbidity Decrease]) showed an excess of deaths (24 vs 10) in the treated group. The trial was stopped. On balance, it seems likely that dronedarone will be as effective as amiodarone, but its overall risk:benefit profile remains to be clearly established.

E-0471 is another analog of amiodarone in which the di-iodophenyl is replaced by a thiophin. Studies in guinea pig myocytes show that it has effects not only in depressing the  $I_{Kr}$  channel, but also the slow and fast components of the delayed rectifier current as well as blocking the L-type Ca channel. An open pilot clinical study showed beneficial effects in patients with atrial arrhythmias.<sup>41,42</sup>

### COMMENTARY

This essay has described the evolution of the Class III antiarrhythmic drugs from their inception in the late 1960s until the present time. The story illustrates the continuing importance of serendipity and clinical observations in the drug discovery process. For example, sotalol was not originally synthesized as a  $\beta$ -blocker, but as part of a structure/function study on the incorporation of alkylsulfonamido groups into the benzene ring of phenylethanolamines.<sup>21</sup> The attractive properties of DL-sotalol for arrhythmia control by a Class III action, as well as for treating angina pectoris and hyperthyroidism, due to its  $\beta$ -blocking properties, were entirely serendipitous observations. Similarly, the amiodarone research program seeking an improved antianginal agent was based on the unsubstantiated efficacy of khellin in angina pectoris.<sup>10</sup> Its Class III actions were

only observed after chronic oral administration to rabbits, necessitated by the poor solubility of amiodarone for acute in vitro studies on cardiac electrophysiology.<sup>4</sup> Furthermore, the reversal of its effects on prolonging action potential duration in rabbit heart by coadministration of thyroxine, as well as its slow onset of effect following oral dosing, are not fully explained even today.<sup>35</sup> Its antiarrhythmic effects were first detected in the clinic and only subsequently did the research scientists in Labaz Laboratories study its acute effects in experimental arrhythmias.<sup>15</sup>

The next phase of the Class III drug evolution was designed drug discovery, based on the reasonable assumption that potent, specific blockade of the  $I_{Kr}$  channel would provide improved antiarrhythmic therapy. This target was made possible by the advances in electrophysiology and patch-clamp technology. Furthermore, the availability of D-sotalol as a chemical template, as well as amiodarone, provided the medicinal chemists with ample opportunities. The currently approved Class III agents (dofetilide/ibutilide) are effective in atrial arrhythmias, but are less effective in controlling serious ventricular arrhythmias.

Nevertheless, Class III agents are more attractive than Class I and Class II because they have minimal negative hemodynamic effects and can be given both orally and parenterally.<sup>43</sup> However, potent highly selective blockade of only the  $I_{Kr}$  channel with concomitant reverse use dependency can be associated with potentially lethal torsades de pointes. The newer antiarrhythmic agents, while termed Class III, have actions on one or more additional cardiac channels (*see Table I*), so the research goals are moving away from pure  $I_{Kr}$  blockade. Perhaps an important lesson to be learned, with application to the whole field of drug discovery, is the pitfall of our tendency



to oversimplify the biological targets, in this case selective  $I_{Kr}$  blockade. This field, like so many others in drug discovery, requires a deeper understanding of the complexity of biological systems.<sup>44</sup> Until this is more feasible, serendipity and translational research, both animal<sup>45</sup> and human,<sup>46</sup> will continue to play a major role.

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