Structure-Activity Relationships and Electrophysiological Effects of Short-Acting Amiodarone Homologs in Guinea Pig Isolated Heart

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ABSTRACT

Antiarrhythmic agents with amiodarone-like electrophysiological actions, but with a more favorable pharmacokinetic profile than amiodarone would be extremely useful for the treatment of many tachyarrhythmias. We designed a series of amiodarone homologs with an alkyl ester group at position 2 of the benzofurane moiety. It was hypothesized that the electrophysiological and pharmacokinetic properties of these compounds are closely related to the size and branching of the ester group. The magnitude and time course of electrophysiological effects caused by methyl (ATI-2001), ethyl (ATI-2010), isopropyl (ATI-2064), sec-butyl (ATI-2042), and neopentyl (ATI-2054) homologs, and their common metabolite (ATI-2000) were investigated in guinea pig isolated heart. In paced hearts (atrial cycle length = 300 ms), each homolog (1 μM) was infused for 90 min followed by a 90-min washout. The stimulus-to-atrium (St-A), atrium-to-His bundle (AH), His bundle-to-ventricle (HV), QRS, and QT intervals, and ventricular monophasic action potential duration at 90% repolarization (MAPD90) were measured every 10 min. ATI-2001 and ATI-2064 significantly lengthened the St-A, HV, and QRS intervals, whereas ATI-2042 and ATI-2054 prolonged only the St-A interval. All compounds except the metabolite prolonged the AH interval. The relative rank order for the homologs to lengthen ventricular repolarization (MAPD90) was ATI-2042 ≥ 2001 = 2010 = 2064 > 2054 ≥ 2000. The metabolite was electrophysiologically inactive. Thus, modification of the benzofurane moiety ester group size and branching markedly altered the magnitude and time course of the electrophysiological effects caused by the ATI compounds. The different structure-activity relationships among the amiodarone homologs may have important consequences for further development of amiodarone-like antiarrhythmic agents.

Among the antiarrhythmic agents, amiodarone has electrophysiological effects that most closely approximate those of the ideal antiarrhythmic agent (Hondeghem and Snyderes, 1990; Guerra et al., 1998). These actions include potassium channel blockade without reverse frequency-dependent activity, calcium and sodium channel antagonism, and non-competitive α- and β-adrenergic receptor antagonism (Hondeghem and Snyderes, 1990; Connolly, 1999). However, amiodarone has a number of side effects, including hepatic, pulmonary, and thyroid toxicity and multiple drug interactions that limit its clinical use (Jafari-Fesharaki and Scheinman, 1998). In addition, one of amiodarone’s primary drawbacks is its complex pharmacokinetic profile, particularly its extremely long half-life (Connolly, 1999). An amiodarone-like agent with a more rapid onset of action and a significantly shorter half-life that still retains the beneficial electrophysiological actions of amiodarone should be a significant addition to the armamentarium of antiarrhythmic drug therapy.

We previously characterized the electrophysiological actions of ATI-2001, a prototype ester homolog of amiodarone with a methyl acetate side chain instead of a butyl on position 2 of the benzofurane moiety (Fig. 1). In guinea pig isolated perfused heart, this compound was found to have
several favorable properties compared with amiodarone (Raatikainen et al., 1996, 2000). First, ATI-2001 was more rapid and effective than amiodarone to slow heart rate, to delay atrioventricular nodal and intraventricular conduction, and to prolong ventricular repolarization. Second, unlike amiodarone, the electrophysiological effects of ATI-2001 were significantly reversed during washout of the drug. Because most of the side effects are closely related to the exceptionally long elimination half-life of amiodarone (Jafari-Fesharaki and Scheinman, 1998), it was speculated that the rapid elimination caused by plasma and tissue esterases would render ATI-2001 less likely to accumulate into tissues and thereby alleviate development of severe adverse events during long-term pharmacotherapy. However, a recent study showing that the half-life of ATI-2001 in human plasma is only 12 min (Juhasz and Bodor, 2000) suggests that the clinical use of ATI-2001 may be restricted to acute termination rather than long-term management of cardiac arrhythmias.

Previously, others have shown that the rate of hydrolysis of ester compounds is inversely related to the length and degree

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**Fig. 1.** Structural formulas of amiodarone (A) and several ATI ester homologs (B). The structural difference between amiodarone and the homolog compounds is that the homologs have a carboxylic acetate side chain in place of butyl on position 2 of the benzofurane moiety (shaded area) of amiodarone. The length and branching of the R position side chains defines the structural differences among the respective ester homologs as noted in B. The molecular weight (M.W.) denotes the value for the base form of each compound. The reported half-lives ($T_{1/2}$) were published previously (Juhasz and Bodor, 2000).
of side chain branching since the bulkier moieties exert steric hindrance of esterase enzymes (Juhasz and Bodor, 2000). Accordingly, we hypothesized that sequential lengthening of the methyl ester side chain at position 2 of the benzoctetrazone moiety of ATI-2001 will lead to greater resistance to ester hydrolysis while still preserving its favorable electrophysiological effects. Therefore, we synthesized a series of homologs of amiodarone by adding methyl groups to the acetate side chain of ATI-2001 to form ethyl (ATI-2010), isopropyl (ATI-2064), sec-butyl (ATI-2042), and neopentyl (ATI-2054) homologs (Fig. 1). In addition, the metabolite (ATI-2000) common to this family of compounds was synthesized for investigation. In this study, we describe the effects of these compounds on several atrial, atrioventricular, and ventricular electrophysiological parameters in guinea pig Langendorff-perfused heart.

Materials and Methods

Chemicals. Stock solutions of ATI-2001 [(methyl-[3-(4-(2-diethylaminoethyl)-3,5-diiodo)benzoyl]benzofuraneacetate], ATI-2010 [(ethyl-[3-(4-(2-diethylaminoethyl)-3,5-diiodo)benzoyl]benzofuraneacetate], ATI-2042 [sec-butyl-[3-(4-(2-diethylaminoethyl)-3,5-diiodo)benzoyl]benzofuraneacetate], ATI-2064 [isopropyl-[3-(4-(2-diethylaminoethyl)-3,5-diiodo)benzoyl]benzofuraneacetate], ATI-2054 [neopentyl-[3-(4-diethylaminoethyl)-3,5-diiodo)benzoyl]benzofuraneacetate], and the metabolite [3-(4-(2-diethylaminoethyl)-3,5-diiodo)benzoyl]benzofuraneacetate] were provided by ARYx Therapeutics, Inc. (Los Altos Hills, CA). The stock solutions were further dissolved in perfusion medium immediately before experimentation.

Isolation, Perfusion, and Pacing of Hearts. All protocols were reviewed and approved by the Animal Use Committee of the University of Florida Health Sciences Center and performed in accordance with the Guide for the Care and Use of Laboratory Animals as adopted and promulgated by the National Institutes of Health. Hartley guinea pigs of either sex weighing 300 to 400 g were anesthetized with halothane (Halocarbon Laboratories, River Edge, NJ) and killed by cervical dislocation. The hearts were rapidly removed and rinsed in ice-cold Krebs-Henseleit (K-H) solution containing 117.9 mM NaCl, 4.8 mM KCl, 2.5 mM CaCl2, 1.2 mM KH2PO4, 0.5 mM Na2EDTA, 2.0 mM MgSO4·7H2O, 1.2 mM CaCl2, 0.5 mM Na2EDTA, 0.14 mM ascorbic acid, 5.5 mM glucose, 2.0 mM pyruvic acid (sodium salt), and 25 mM NaHCO3. The ascending aorta was cannulated for perfusion of the coronary arteries at a constant flow of 8 ml/min with K-H solution gassed continuously with 95% O2, 5% CO2. The oxygen tension, temperature, and pH of the K-H solution were maintained at 500 to 600 mm Hg, 36.0 ± 0.5°C, and 7.3 to 7.4, respectively.

Hearts were paced using an interval generator (A310 Accumulser; World Precision Instruments, Sarasota, FL) that delivered stimuli via a stimulus isolation unit (A360R; World Precision Instruments) as square wave pulses of 3-ms duration and twice threshold intensity. The stimuli were delivered at a basic cycle length of 300 ms via a stainless steel, Teflon-coated, bipolar electrode placed on the epicardium of the left atrium. After completion of dissection and instrumentation the hearts were allowed to equilibrate for 30 min before experiments commenced.

Extracellular Electromgrams and Monophasic Action Potential Recordings. Electromgrams were recorded using a unipolar electrode placed on the surface of the left atrium and in the His bundle region (Martynyuk et al., 1999). Monophasic action potentials (MAP) were recorded using a pressure contact silver-silver chloride electrode (EP Technologies, Inc., Sunnyvale, CA) placed on the epicardial surface of the left ventricle as previously described (Raatikainen et al., 1996). Signals were amplified and filtered using an isolated biological amplifier (IsoDam; World Precision Instruments); digi-

Results

Effects on Cardiac Conduction

Atrial Conduction. ATI-2001 and ATI-2042 prolonged the St-A interval to a greater extent than did ATI-2064 and ATI-2054, whereas ATI-2010 and the metabolite did not significantly affect atrial conduction (Fig. 2; Table 1). The mean St-A interval value among all groups was 11.7 ± 0.4 ms and did not vary between groups. Over the 90-min infusion period, the average increase of the St-A interval was 2.2 ± 0.1, 1.8 ± 0.3, 1.1 ± 0.3, and 0.7 ± 0.1 ms for ATI-2001 (P < 0.001), ATI-2042 (P < 0.001), ATI-2054 (P = 0.015), and ATI-2064 (P < 0.001), respectively. In contrast, neither ATI-2010 (P = 0.365) nor the metabolite (P = 0.997) increased the St-A interval. Following discontinuation of drug infusion, the effects of ATI-2001 and ATI-2064 significantly decreased by 150 and 130 min, respectively, whereas the atrial conduction delay caused by ATI-2042 persisted.
Atrioventricular Nodal Conduction. All the ATI compounds except for the metabolite significantly prolonged the AH interval (Fig. 3; Table 1). The mean AH interval value during control conditions was 45.6 ± 1.2 ms and did not vary among hearts treated with different drugs. During the 90-min drug infusion period, the mean increase in the AH interval was 18.9 ± 1.4, 18.3 ± 1.5, 17.8 ± 2.5, 9.1 ± 1.1, and 6.1 ± 0.7 ms for ATI-2001 (P < 0.001), ATI-2064 (P < 0.001), ATI-2042 (P < 0.001), ATI-2010 (P = 0.016), and ATI-2054 (P < 0.027), respectively. The times for these drugs to achieve peak effects on the AH intervals were 120 min (ATI-2001), 90 min (ATI-2010), 140 min (ATI-2042), 170 min (ATI-2054), and 110 min (ATI-2064). During washout, the effects of ATI-2010 completely reversed at time 130 min. The prolongation caused by ATI-2001 and ATI-2064 tended to washout, whereas the delay in AV nodal conduction caused by ATI-2042 continued to increase.

His-Purkinje Conduction. Only ATI-2001 and ATI-2064 significantly prolonged the HV interval during the 90-min drug infusion period (Fig. 4; Table 1). The mean HV interval during control conditions was 10.3 ± 0.3 ms and did not differ between groups. The mean HV interval increase caused by a 90-min infusion of ATI-2064 (P < 0.001), ATI-2001 (P < 0.001), the metabolite (P = 0.397), ATI-2042 (P = 0.516), ATI-2010 (P = 0.791), and ATI-2054 (P = 0.653) was 2.5 ± 0.3, 2.0 ± 0.3, 1.3 ± 0.1, 0.9 ± 0.2, 0.7 ± 0.2, and 0.5 ± 0.1 ms, respectively. Following cessation of drug infusion, the changes caused by ATI-2064 significantly dissipated by 170 min, whereas the increase caused by ATI-2001 tended to diminish.

Intraventricular Conduction. Similar to those changes observed for the HV interval, only ATI-2001 and ATI-2064 caused significant delays in intraventricular conduction during the 90-min drug infusion (Fig. 5; Table 1). The mean control QRS interval value was 22.2 ± 0.6 ms and did not differ between groups. ATI-2001 (P < 0.001) and ATI-2064 (P < 0.001) increased the QRS interval over the time of drug infusion, whereas ATI-2010 (P = 0.632), ATI-2054 (P = 0.999), ATI-2042 (P = 0.129), and the metabolite (P = 1.000) had no effect on intraventricular conduction. The mean QRS increase caused by ATI-2001 and ATI-2064 was 3.8 ± 0.7 and 2.2 ± 0.7 ms, respectively. The effects of ATI-2001 completely dissipated by 150 min, whereas the effects caused by ATI-2064 persisted for the whole washout period.

Fig. 2. Time course and analysis of the effects of several ester homologs of amiodarone on the AH interval measured in guinea pig isolated heart. Each compound (1 μM) was infused into hearts for 90 min (0–90 min) followed by a 90-min washout period (90–180 min). Horizontal bar indicates duration of drug infusion. Data expressed as mean ± S.E.M. of four to seven hearts per homolog.

Fig. 3. Time course of the negative dromotropic effects of several ester homologs of amiodarone on the AH interval measured in guinea pig isolated heart. Each compound (1 μM) was infused into hearts for 90 min (0–90 min) followed by a 90-min washout period (90–180 min). Horizontal bar indicates duration of drug infusion. Data expressed as mean ± S.E.M. of four to seven hearts per homolog.

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Fig. 4. Time course of the effects of several ester homologs of amiodarone on the AH interval measured in guinea pig isolated heart. Each compound (1 μM) was infused into hearts for 90 min (0–90 min) followed by a 90-min washout period (90–180 min). Horizontal bar indicates duration of drug infusion. Data expressed as mean ± S.E.M. of four to seven hearts per homolog.

Table 1

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Rank Order</th>
</tr>
</thead>
<tbody>
<tr>
<td>St-A</td>
<td>ATI-2001 &gt; ATI-2042 &gt; ATI-2054 &gt; ATI-2064 &gt; ATI-2010 = metabolite</td>
</tr>
<tr>
<td>AH</td>
<td>ATI-2001 = ATI-2064 = ATI-2042 = ATI-2010 = ATI-2054 = metabolite</td>
</tr>
<tr>
<td>HV</td>
<td>ATI-2064 = ATI-2001 = metabolite = ATI-2042 = ATI-2010 = ATI-2054 = metabolite</td>
</tr>
<tr>
<td>QRS</td>
<td>ATI-2001 &gt; ATI-2064 &gt; ATI-2042 &gt; ATI-2010 = ATI-2054 = metabolite</td>
</tr>
<tr>
<td>QT</td>
<td>ATI-2042 = ATI-2001 &gt; ATI-2064 = ATI-2010 &gt; ATI-2054 = metabolite</td>
</tr>
<tr>
<td>MAPD90</td>
<td>ATI-2042 ≥ ATI-2001 = ATI-2010 = ATI-2064 &gt; ATI-2054 ≥ metabolite</td>
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Effects on Ventricular Repolarization

QT Interval. Although the metabolite and ATI-2054 did not prolong repolarization, the other homologs significantly prolonged the QT interval (Fig. 1; Table 1). The mean QT interval was 189.1 ± 1.3 ms and did not statistically differ between compounds. Infusion of ATI-2001 (P < 0.0001), ATI-2010 (P = 0.010), ATI-2042 (P < 0.001), and ATI-2064 (P = 0.050) increased the mean QT interval by 12.7 ± 1.0, 7.4 ± 0.9, 15.1 ± 1.2, and 5.3 ± 1.1 ms, respectively. In contrast, ATI-2054 (P = 0.988) and the metabolite (P = 0.965) caused no change in the QT interval. The effects of ATI-2001, ATI-2010, ATI-2042, and ATI-2064 on the QT interval were sustained following cessation of drug infusion.

MAPD\textsubscript{90} Repolarization. In general, the changes caused by the homologs on MAPD\textsubscript{90} (Fig. 7; Table 1) were similar to those observed on the QT interval (Fig. 6). The mean MAPD\textsubscript{90} value for all hearts was 166.0 ± 1.4 ms and did not statistically differ between groups. During the washout period, ATI-2001 (P < 0.001), ATI-2010 (P = 0.007), and ATI-2042 (P < 0.001) prolonged the MAPD\textsubscript{90} by an average of 7.3 ± 1.0, 5.3 ± 0.8, and 10.4 ± 1.1 ms, respectively, whereas ATI-2054 (P = 0.978), ATI-2064 (P = 0.107), and the metabolite (P = 0.726) caused no significant effects. Following cessation of drug infusion, the effects of ATI-2042 and ATI-2064 continued to increase. Similarly, ATI-2064 greatly delayed repolarization during the washout period (P < 0.001) with a significant increase at 140 min compared with 90 min. A summary of the relative effects of these drugs on these electrophysiological parameters is shown in Fig. 8.

Discussion

In an effort to overcome the complex pharmacokinetic properties and toxic side effects of amiodarone, a number of amiodarone-related compounds have recently been developed (Raatikainen et al., 1996, 2000). In this study, we characterized the acute electrophysiological effects of several short-acting ester derivatives of amiodarone. The main findings were 1) the magnitude and time course of the electrophysiological actions of the prototype homolog ATI-2001 were markedly altered by serial enlargement (lengthening and branching) of the side chain at position 2 of the benzofuran moiety, and 2) the metabolite (ATI-2000) common to all the ATI compounds caused no significant electrophysiological actions.

Structure-Activity Relationships and Electrophysiological Effects

Even subtle modifications of a drug’s molecular structure (e.g., d- versus l-sotalol) may dramatically alter the electrophysiological properties of that agent (Holubarsch et al., 1995). We found a close link between the size (length and branching) of the ester group and the magnitude and time course of the electrophysiological actions of the ATI series of compounds. Three separate lines of evidence support the concept that distinct structure-activity relationships exist among the ATI homologs. First, addition of a methyl group to the methyl side chain of the highly active prototype homolog (ATI-2001) created an ethyl derivative (ATI-2010) that possessed virtually no electrophysiological activity. Second, as the ester group of ATI-2001 was further lengthened by sequential addition of methyl groups, the acute electrophysiological effects of the compounds became progressively slower to develop and ultimately disappeared when the ester side chain contained five carbons (ATI-2054, neopentyl). Interestingly, the magnitude and time-dependent nature of the electrophysiological activity of the compound with a four (ATI-2042) or three (ATI-2064) carbon side chain closely resembled those reported for amiodarone (Raatikainen et al., 1996). Third, removal of the ester side chain from the homologs to create the common metabolite (ATI-2000) was associated with loss of electrophysiological activity. The finding that the metabolite of the ATI compounds has no electrophysiological activity is a highly desirable feature. In contrast, the principal metabolite of amiodarone, desethylamiodarone, is electrophysiologically active and possesses an even longer elimination half-life (31–110 days) than does amiodarone (Staubli et al., 1985; Stark et al., 1991).

Although the exact reasons for the pharmacokinetic differences between the homologs are unknown, both physicochemical properties (e.g., lipophilicity and/or tissue binding of the compounds), and susceptibility to enzymatic degradation (e.g., steric hindrance due to tissue esterases caused by a larger side chains) are likely etiologies. In keeping with the latter point, enzymatic hydrolysis of ATI homologs containing small ester chains was much faster than those with larger groups in human plasma (Juhasz and Bodor, 2000). Likewise, ATI-2054 was less efficacious and had a much slower onset of action than ATI-2042 or ATI-2064 to terminate stress-induced ventricular arrhythmias or to change cardiac conduction and/or repolarization in anesthetized rats (Juhasz and Bodor, 2000).

Effects on Atrial and Ventricular Conduction. Like amiodarone, most of the ATI compounds prolonged atrial, His Purkinje, and intraventricular conduction. For amiodarone, the class I action is consistent with sodium channel blockade and has been associated both with high antiarrhythmic efficacy and low proarrhythmogenicity. Frequency-dependent block of cardiac sodium conductance not only enhances amiodarone’s class III antiarrhythmic efficacy by providing additional lengthening of refractoriness (i.e., postrepolarization refractoriness) (Sicilian Gambit, 1991; Sager et al., 1993), but also decreases the likelihood of developing arrhythmias such as torsades de pointes (Hohnloser et al., 1994; Lee et al., 1997). In keeping with this and despite having significant sodium channel blocking activity, amiodarone improves left ventricular ejection fraction and reduces the risk of sudden cardiac death in patients with structural heart disease (Massie et al., 1996; Farre et al., 1999). The exact reasons for these findings are unknown, but are probably attributable to the complex spectrum of electrophysiological actions of amiodarone and the nature of the sodium channel block (Sicilian Gambit, 1991; Singh, 1998). Taken together, we expect that any sodium channel block in the setting of amiodarone-like antiarrhythmic activity such as with the ATI compounds is safe and important for their clinical efficacy.

Effects on AV Nodal Conduction. Agents that prolong (or block) AV nodal conduction either by suppressing the L-type calcium current (I_{Ca,L}) or by activating the acetylcholine- and adenosine-sensitive potassium current (I_{K,ACH,Ado}) effectively terminate reentrant tachycardias involving the AV node and control ventricular rate during supraventricular arrhythmias such as atrial fibrillation (Ganz and Fried-
Whether these data can be extrapolated to the ATI compounds remains to be established. Nevertheless, all ATI compounds significantly delayed AV nodal conduction with the exception of the metabolite that had no significant effect.

**Effects on Ventricular Repolarization.** Like amiodarone (Connolly, 1999), some of the ATI compounds delayed ventricular repolarization, as evidenced by lengthening of MAPD$_{90}$ and QT interval. By prolonging refractoriness, class III antiarrhythmic agents are particularly effective at terminating reentrant tachyarrhythmias where conduction encroaches on refractoriness (short excitable gap) such as ventricular fibrillation (Sicilian Gambit, 1991). However, the mechanisms whereby class III antiarrhythmic agents cause proarrhythmic effects cannot be separated from their antiarrhythmic actions. For example, the suppression of potassium conductance that prolongs repolarization and refractoriness may also cause torsades de pointes, a type of ventricular tachycardia that is often preceded by abrupt slowing of heart rate that provokes development of early afterdepolarization (El-Sherif et al., 1989). Compared with the “pure” class III agents, amiodarone rarely causes torsades de pointes (Hohnloser et al., 1994). We hypothesize that the absence of reverse frequency-dependent effect on ventricular repolarization and refractoriness caused by the prototype homolog ATI-2001 (Raatikainen et al., 1996) may be common to all ATI compounds and thereby results in amiodarone-like efficacy and low incidence of proarrhythmic action.

**Limitations**

This study was specifically designed to determine the time course of the acute electrophysiological effects of these homologs in the isolated perfused heart. Therefore, we cannot comment on the bioavailability of the drugs, potential interactions with autonomic nervous system, or actions that may accompany long-term treatment with an ATI series drug. The duration of therapy with these homologs may be important in light of the well known effects between acute versus chronic amiodarone therapy. Similarly, differences in potencies among the compounds cannot be definitively stated because measurements were not steady-state effects. Although concentration-response relationships are always preferable, the slow development of electrophysiological effects limited us to study only a single concentration (1 μM). Lastly, be-
cause both amiodarone and the ATI compounds have a high iodine content and amiodarone causes thyroid toxicity, it remains to be established whether chronic pharmacotherapy with the much shorter acting ATI homologs causes similar adverse reactions. Regardless, this experimental paradigm allowed us to delineate distinct structure-activity relationships among the ATI series and provided direction as to which compound(s) merits consideration for future development.

Clinical Implications and Future Directions

As a consequence of the disappointing results of previous clinical trials (CAST Investigators, 1989; Waldo et al., 1996), the major clinical and investigative effort in the control of ventricular arrhythmias has been shifting away from agents that selectively prolong ventricular conduction or repolarization to more complex agents. Because of its high efficacy and low proarrhythmic potential, amiodarone is generally considered the most effective antiarrhythmic agent (Singh, 1998). Unfortunately, however, some pharmacokinetic shortcomings and toxic side effects markedly limit the clinical use of amiodarone (Jafari-Fesharaki and Scheinman, 1998). Although intravenous amiodarone is the only antiarrhythmic agent that has been shown to improve resuscitation of patients who suffered out-of-hospital cardiac arrest due to ventricular arrhythmias (Kudenchuk et al., 1999), it is widely accepted that the slow onset of the class III action limits its acute efficacy. Therefore, an intravenous amiodarone-like agent such as ATI-2001, ATI-2042, or ATI-2064 having a more rapid onset of electrophysiological action than amiodarone would have a significant impact on acute management of various ventricular and supraventricular tachyarrhythmias. Moreover, the major metabolite (ATI-2000) of the ATI derivatives was electrophysiologically inactive in contrast to the significant activity caused by desethylamiodarone.

In conclusion, these results clearly demonstrate how structural modifications of a molecule to prolong its half-life must always be directly balanced against retention of its pharmacological activity. That is, among the homologs tested, the one with the longest half-life in human plasma, ATI-2054, lacked electrophysiological activity and is therefore not suitable for further drug development. The rank order of equimolar concentrations of the compounds to alter cardiac electrophysiological parameters and the time courses of action combined in the previously reported half-lives of the ATI compounds in human plasma (Juhasz and Bodor, 2000) suggest that ATI-2042 (sec-butyl) and ATI-2064 (isopropyl) merit further investigations to evaluate their safety and efficacy for chronic antiarrhythmic therapy, whereas the clinical use of the prototype homolog ATI-2001 is likely to be restricted to acute arrhythmia management.

References


