Potent and Reversible Effects of ATI-2001 on Atrial and Atrioventricular Nodal Electrophysiological Properties in Guinea Pig Isolated Perfused Heart

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ABSTRACT

We recently demonstrated that the short-acting analog of amiodarone, ATI-2001, caused favorable effects in guinea pig ventricular myocardium on electrophysiological substrates underlying tachyarrhythmia initiation, perpetuation, and termination. Here, the acute effects of 1.0 μM ATI-2001 and 1.0 μM amiodarone (90-min infusion followed by 90-min washout period) on atrial and atrioventricular (AV) nodal electrophysiological properties were studied in guinea pig isolated hearts. Neither ATI-2001 nor amiodarone significantly prolonged atrial conduction time. Compared with amiodarone, ATI-2001 caused significantly more rapid and greater prolongation of atrial monophasic action potential duration at 90% repolarization (maximal change 21.4 ± 3.7 versus 19.0 ± 4.0 ms) and atrial effective refractory period (ERP, 27.8 ± 6.1 versus 9.2 ± 2.3 ms). Shortening of the atrial cycle length from 250 to 200 ms did not significantly alter drug-induced changes in atrial repolarization and refractoriness. ATI-2001 prolonged the atrium-to-His bundle interval (22.1 ± 2.6 versus 8.8 ± 2.3 ms), His bundle-to-ventricle interval (2.8 ± 0.4 versus 0.9 ± 0.3 ms), AV nodal ERP (72.5 ± 7.3 versus 31.4 ± 4.1 ms), and Wenckebach cycle length (69.6 ± 5.2 versus 35.8 ± 4.1 ms) significantly more than did amiodarone. Unlike amiodarone, the effects of ATI-2001 were markedly reversed upon discontinuation of drug infusion. Given these data, ATI-2001 should not only be useful for terminating ongoing and preventing recurrence of atrial tachyarrhythmias but also to treat supraventricular tachycardias involving the AV node and to control ventricular rate during atrial tachyarrhythmias. Whether the observed differences in the pharmacokinetic properties render ATI-2001 superior to amiodarone in acute tachyarrhythmia management and less likely to accumulate into tissues during chronic therapy remains to be established.

The major goal in the pharmacotherapy of supraventricular tachyarrhythmias is termination of ongoing arrhythmia and prevention of its reoccurrence (Levy et al., 1998). In patients with atrial fibrillation or flutter in whom normal sinus rhythm cannot be restored, regulation of ventricular rate by agents that delay atrioventricular (AV) nodal conduction and prolong refractoriness becomes the main therapeutic goal (Prystowsky et al., 1996; Blitzer et al., 1998; Levy et al., 1998). Among currently available antiarrhythmic agents, amiodarone seems to be the most effective drug to prevent atrial arrhythmias (Nattel, 1995; Kassotis et al., 1998). Although the role of amiodarone in the long-term management of atrial and ventricular tachyarrhythmias is well entrenched in clinical practice, its side effect profile remains a serious concern (Vrobel et al., 1989; Vorperian et al., 1997). Furthermore, the usefulness of amiodarone for acute management of atrial arrhythmias is somewhat limited by its complex pharmacokinetic properties and slow development of class III effect (Roden, 1993; Podrid, 1995; Kodama et al., 1997).

During recent years various analogs of the prototypical compound have been developed to overcome the side effects of amiodarone (Raatikainen et al., 1996; Kulier et al., 1999; Sun et al., 1999). ATI-2001 is a novel ester analog of amiodarone. The molecular structure of ATI-2001 is identical with that of amiodarone, except for the presence of a methyl acetate side chain in lieu of butyl group at position 2 of the benzofurane.

ABBREVIATIONS: AV, atrioventricular; HBE, His bundle electrogram; MAP, monophasic action potential; S-A, stimulus-to-atrium interval; A-H, atrium-to-His bundle interval; H-V, His bundle-to-ventricle interval; BCT, basal conduction time; MAPD 90, monophasic action potential duration at 90% repolarization; ERP, effective refractory period; WCL, Wenckebach cycle length; ACL, atrial cycle length.
moiety (Raatikainen et al., 1996). This structural modification renders ATI-2001 susceptible to metabolism by plasma and tissue esterases and thus accelerates its elimination from blood and body organs. In keeping with this premise, we recently demonstrated in guinea pig isolated perfused heart that, unlike amiodarone, the effects of ATI-2001 on ventricular conduction delay, repolarization, and refractoriness were markedly reversed during washout of the drug. The effects of ATI-2001 on ventricular electrophysiological properties were also more rapid to develop, and more potent than those of an equimolar concentration of amiodarone (Raatikainen et al., 1996). Although the electrophysiological effects of ATI-2001 in supraventricular tissues remained mostly uncharacterized, our preliminary findings suggested that ATI-2001 might exert antiarrhythmic actions also in the atria and AV node.

Once initiated, atrial fibrillation can rapidly modify atrial electrical properties in a way that promotes perpetuation of the arrhythmia, a process called atrial remodeling (Wijffels et al., 1995). These changes include shortening of atrial refractoriness and loss of normal adaptation to rate. Because atrial remodeling can develop after only a few hours of atrial fibrillation, rapid termination is a highly desirable therapeutic goal. Development of an agent with amiodarone-like properties that has a more rapid onset of action would not only be useful to terminate atrial fibrillation, but also to prevent the long-term consequences of atrial remodeling.

Electrophysiological parameters critical to initiation, perpetuation, and termination of atrial tachyarrhythmias and to regulation of ventricular rate during such arrhythmias include alteration of atrial conduction velocity, repolarization, and refractoriness (Rensma et al., 1988; Janse, 1997), and modulation of AV nodal conduction properties (Meijler et al., 1996), respectively. In the present study, we determined the effects of ATI-2001 on atrial conduction time, monophasic action potential duration, and effective refractory period, and on frequency-dependent AV nodal conduction delay in guinea pig isolated perfused hearts. The changes caused by ATI-2001 are compared with those of the prototypic compound amiodarone.

**Materials and Methods**

**Chemicals**

ATI-2001 (methyl 2-[3-(4-(2-diethylaminoethoxyl)-3,5-diiodo-)benzoyl] benzofuranacetate) was a gift from ARYx Therapeutics (Los Altos Hills, CA). Amiodarone and all the chemicals used for the Krebs-Henseleit perfusion medium were purchased from Sigma Chemical Co. (St. Louis, MO). Stock solutions (10 mM) of ATI-2001 and amiodarone were prepared in pure ethanol and further dissolved in perfusion medium immediately before experimentation.

**Isolated Perfused Hearts**

All experimental protocols were reviewed and approved by the Animal Use Committee of the University of Florida Health Sciences Center. The hearts were isolated from Hartley guinea pigs of either sex, weighing 400 to 450 g, and perfused according to the Langendorff technique as previously described (Napolitano et al., 1996). After completion of dissection and instrumentation, the hearts were allowed to equilibrate for at least 20 to 30 min before the experimental protocols were begun. Unless otherwise indicated, the hearts were paced (square-wave 3-ms pulses at twice threshold intensity) at an atrial cycle length of 250 ms via a bipolar electrode placed on the high atrioseptal area.

**Electrophysiological Techniques and Measurements**

During the experiments the His bundle electrogram (HBE) and left atrial monophasic action potentials (MAP) were displayed in real time and digitally stored at a sampling frequency of 2 kHz using a Digidata 1200A analog-to-digital data acquisition board (Axon Instruments Inc., Foster City, CA) and Axotape data acquisition program (Axon Instruments Inc.) as detailed previously (Morey et al., 1997).

HBE. The HBE was recorded using a unipolar Teflon-coated stainless steel electrode placed in the His bundle position through a small right atrial incision as previously described (Jenkins and Belardinelli, 1988). The stimulus-to-atrium (S-A), atrium-to-His bundle (A-H), and His bundle-to-ventricle (H-V) intervals were used as indices of intra-atrial, AV nodal (proximal AV), and His Purkinje system (distal AV) conduction times, respectively. Intervals were measured from digitally stored HBE using cursor measurements in the Axotape program. In the event that an intervention caused a second or third degree AV block, the longest stable A-H interval just before the onset of AV block was considered the maximum dromotropic effect, and that value was used for data analysis.

MAPs. The MAP was recorded with a pressure contact silver-silver chloride electrode (EP Technologies, Sunnyvale, CA) positioned in the immediate vicinity of the pacing electrode on the epicardial surface of the left atrium as previously described (Raatikainen et al., 1998). Signals were considered adequate if their amplitudes (from diastolic baseline to plateau) exceeded 8 mV. The basal conduction time (BCT) and duration of the MAP at 90% repolarization (MAPD90) were measured using a custom-made computer template written for Microsoft Excel 7.0 (Microsoft Corporation, Redmond, WA).

Effective Refractory Periods (ERPs) and Wenckebach Cycle Length (WCL). Atrial ERP, AV nodal ERP, and WCL were measured using previously described computer-assisted stimulation protocols (Napolitano et al., 1996; Raatikainen et al., 1998). Briefly, atrial and AV nodal ERPs were measured simultaneously using a premature stimulation protocol in which the coupling interval between the last basic stimulus (S1) and the extra stimulus (S2) was progressively shortened by 3 ms after every train of 15 basic stimuli (S1S2). The longest S1S2 that failed to produce an atrial response (A2) and His bundle (H2) was defined as the atrial and AV nodal ERP, respectively. WCL was determined as the longest ACL that failed to conduct through the AV node and produce a His bundle response (second degree block) during a run in which the basic atrial cycle length was decreased in 3-ms steps after every 10 basic stimuli. If a drug caused second degree AV block during baseline stimulation, the basic cycle length was considered the AV nodal ERP and WCL.

**Pharmacological and Pacing Protocols**

**Drug Infusion.** The concentration of drugs chosen was 1.0 μM, based on our previous experiments (Raatikainen et al., 1996) and the following clinical observations. The average steady-state plasma concentration of amiodarone has been 0.9 to 2 μM among the majority of successfully treated patients, whereas the reported concentration for those with side effects has usually been greater than 3 μM (Rotmensch et al., 1984). Because some of the electrophysiological effects of amiodarone are slow to develop and slow to disappear (Rodén, 1993; Podrid, 1995; Kodama et al., 1997), we elected to compare the time-dependent actions of equimolar drug concentrations over a relatively long drug infusion (90 min) and washout period (90 min) instead of trying to construct a true concentration-response curves for ATI-2001 and amiodarone. After baseline electrograms were recorded, the hearts were randomly treated for 90 min with either 1.0 μM ATI-2001 or 1.0 μM amiodarone. Thereafter, the drugs were washed out for another 90 min. In our previous study (Raatikainen et al.,...
Effects on Atrial Conduction Time, Repolarization, and Refractoriness. The effects of ATI-2001 and amiodarone on atrial conduction time, measured as the S-A interval from the continuously recorded HBE, are shown in Fig. 1. Neither ATI-2001 nor amiodarone significantly prolonged the S-A interval and the BCT (data not shown). All the above-mentioned electrophysiological parameters were measured both during the baseline stimulation (ACL = 250 ms) and during a faster atrial pacing rate (ACL = 200 ms). In a subset of hearts, a slower rate of atrial pacing (ACL = 300 ms) was used to further evaluate the frequency dependence of the AV nodal effects of the drugs. In these experiments, atrial MAP recordings were precluded because the atria had to be almost completely excised to facilitate pacing at the slower rate.

Data Analyses
All values are expressed as mean ± S.E. of 6 to 10 experiments. Statistical differences among mean values were analyzed using ANOVA (one- or two-way when appropriate) followed by Tukey testing. P < .05 was considered statistically significant.

Results
Effects on Atrial Conduction Time, Repolarization, and Refractoriness. The effects of ATI-2001 and amiodarone on atrial conduction time, measured as the S-A interval from the continuously recorded HBE, are shown in Fig. 1. Neither ATI-2001 nor amiodarone significantly prolonged the S-A interval and the BCT (data not shown) in hearts paced at a constant atrial cycle length of 250 ms. The maximum prolongation of the S-A interval caused by ATI-2001 and amiodarone was 18.3 ± 6.2% (P = .33) and 7.40 ± 5.3% (P = .94), respectively. Upon discontinuation of the drug infusion, the effects of ATI-2001 tended to return toward baseline, whereas in the amiodarone-treated hearts the atrial conduction time continued to increase. Shortening of the basic ACL from 250 to 200 ms had no significant effect on the effect of the drugs on atrial conduction time (data not shown).

The effects of ATI-2001 and amiodarone on atrial MAP duration at 90% repolarization (MAPD90), and on atrial ERP in hearts paced at 250-ms basic atrial cycle length are depicted in Figs. 2 and 3, respectively. At a concentration of 1.0 μM, ATI-2001 prolonged atrial MAPD and ERP more rapidly and to a greater extent than did amiodarone. That is, the drug-induced prolongation of the MAPD90 achieved statistical significance after 30- and 60-min infusion times in the ATI-2001 and amiodarone groups, respectively. The maximum prolongation of atrial ERP was 34.0 ± 8.3% in ATI-2001-treated hearts, but only 10.9 ± 2.9% (P < .01) in amiodarone-treated hearts. The threshold for a significant change in atrial ERP was 30 min for the ATI-2001 group, whereas in the amiodarone group no significant change occurred during the 90-min drug infusion period. Upon cessation of the drug infusion the effect of ATI-2001 on atrial repolarization and refactoriness was partially reversed. In contrast, the prolongation of atrial MAPD and ERP caused by amiodarone continued to increase during the whole washout period.

A decrease of the basic ACL from 250 to 200 ms did not significantly affect the atrial electrophysiological effects of ATI-2001 or amiodarone. That is, a 90-min infusion of ATI-2001 prolonged atrial MAPD90 and ERP by approximately 30% at both the slower (ACL = 250 ms) and faster (ACL = 200 ms) atrial pacing rates (Fig. 4). Amiodarone also prolonged atrial repolarization and refactoriness in a relatively frequency-independent manner, but to a lesser extent than that of ATI-2001.

Effects on AV Nodal Conduction Time. Compared with an equimolar concentration of amiodarone (1.0 μM), ATI-2001 caused significantly more rapid and greater prolongation of the A-H interval (Fig. 5). In the ATI-2001 group, prolongation of the A-H interval reached statistical significance after a 30-min infusion time. In contrast, amiodarone did not significantly change the A-H interval during the 90-min drug infusion period (the A-H interval continued to increase after stopping of the infusion). At the end of the 90-min drug infusion period, the A-H interval prolongation was 69% (from 33.1 ± 2.3 to 55.2 ± 2.3 ms) and 26% (from 33.3 ± 1.4 to 42.1 ± 3.2 ms) above baseline values in the ATI-2001- and amiodarone-treated hearts, respectively. Unlike amiodarone, the effects of ATI-2001 were readily reversible upon discontinuation of the drug infusion. In the ATI-2001 group, the A-H interval shortened from the maximum value of 55.2 ± 2.3 to 43.6 ± 3.3 ms during the washout period.

**Fig. 1.** Time-dependent effects of ATI-2001 and amiodarone on atrial conduction time. Neither ATI-2001 (P = .33) nor amiodarone (P = .94) caused a significant prolongation of the S-A interval. Each data point represents the mean ± S.E. of six hearts paced at a basic atrial cycle length of 250 ms.

**Fig. 2.** Time-dependent effects of ATI-2001 and amiodarone on atrial monophasic action potential duration at 90% repolarization (MAPD90). Both ATI-2001 and amiodarone significantly prolonged atrial MAPD90. The effect of ATI-2001 was more rapid to develop than that of amiodarone. Each data point represents the mean ± S.E. of six hearts paced at a basic atrial cycle length of 250 ms. P < .05: *, versus baseline.
In contrast, the prolongation of the A-H interval caused by amiodarone continued to increase after the drug infusion was discontinued, reaching a maximal increase of 46% above baseline at the end of experimentation. Although not statistically significant, there was a trend for amiodarone and in particular for ATI-2001 to also increase conduction time over the His-Purkinje system. ATI-2001 and amiodarone prolonged the H-V interval from 11.1 ± 0.7 ms and 11.0 ± 0.9 ms to 13.9 ± 0.9 ms (25% increase above baseline, \( P = .08 \)) and 11.9 ± 1.1 ms (8% increase above baseline, \( P = .476 \)), respectively. Similar to those results observed on the A-H interval, the action of ATI-2001 but not that of amiodarone appeared to reverse after discontinuation of the drug infusion (Fig. 6).

Frequency-Dependent Negative Dromotropic Effect on the AV Node. As predicted by the A-H interval changes, ATI-2001 caused greater prolongation of AV nodal ERP (maximal prolongation above baseline values 72.5 ± 7.3 versus 31.4 ± 4.1 ms, \( P < .001 \)) and WCL (maximal prolongation above baseline values 69.6 ± 5.2 versus 35.8 ± 4.1 ms, \( P < .001 \)) than did an equimolar concentration of amiodarone. Furthermore, these effects of ATI-2001 were rapidly reversed upon discontinuation of the drug, whereas those of amiodarone continued to increase (Figs. 7 and 8). A third line of evidence supporting the frequency-dependent negative dromotropic action of ATI-2001 and amiodarone is shown in Fig. 9. At a basic atrial cycle length of 200, 250, and 300 ms, a 90-min infusion of 1 \( \mu \)M ATI-2001 caused high degree AV nodal block in 83, 16, and 0% of the hearts, respectively. These data also unequivocally show that the onset of ATI-2001’s action on AV nodal conduction was faster than that of amiodarone. For example, a 30-min infusion of ATI-2001 or amiodarone caused high degree AV nodal block in 67 and 0%, respectively, of the hearts paced at a 200-ms atrial cycle length. Taken together, these data indicate that the negative...
The dromotropic effects of ATI-2001 and amiodarone were frequency dependent.

**Discussion**

In the present study, we characterized the acute effects of a novel analog of amiodarone, ATI-2001, on atrial and AV nodal electrophysiological properties in guinea pig isolated perfused hearts. Although we observed significant differences in the effects of these two agents, the actions of ATI-2001 were generally similar to those of the prototypical compound amiodarone. That is, during a relatively short infusion time they both prolonged atrial repolarization and AV nodal conduction time. Their effects on atrial repolarization and refractoriness seemed to be frequency independent during slow and faster atrial pacing rates, whereas their negative dromotropic action in the AV node was highly frequency dependent (significantly augmented upon shortening of the ACL). The main differences between the drugs were as follows: 1) the onset of action and washout of the electrophysiological effects were faster in hearts treated with ATI-2001 than with those administered amiodarone; and 2) the maximal electrophysiological changes caused by ATI-2001 were greater than those caused by an equimolar concentration of amiodarone.

**Atrial Effects**

Most sustained atrial arrhythmias (e.g., atrial fibrillation) are caused by reentrant excitation (Janse, 1997). Electrophysiological parameters critical to the development and perpetuation of reentrant tachycardias are changes in atrial conduction velocity, repolarization, and refractoriness (Rensma et al., 1988; Janse, 1997). Antiarrhythmic drugs that effectively terminate and prevent the reoccurrence of atrial arrhythmias either impair conduction (class I action) or prolong repolarization (class III action) in atrial tissue. Ideally, an antiarrhythmic agent should demonstrate frequency-dependent antiarrhythmic action (i.e., have the greatest effect during tachycardia and minimal-to-no effect during normal sinus rhythm). Subsequently, the effects of ATI-2001 on these electrophysiological factors are discussed and compared with those actions of the prototypical compound amiodarone.

**Atrial Conduction.** In the current study, neither ATI-2001 nor amiodarone significantly prolonged atrial conduction times. Although not statistically significant, ATI-2001 tended to prolong the S-A interval more than did amiodarone (25 versus 8% prolongation). Interestingly, there was a tendency of the S-A interval to continue to increase even after the infusion of amiodarone was discontinued, whereas the effects of ATI-2001 were almost totally reversed after cessation of the drug. These findings are in accordance with previous results from our laboratory (Raatikainen et al., 1996), and indicate that ATI-2001 possesses some class I activity. For amiodarone the class I antiarrhythmic action has been associated with antiarrhythmic potential, especially in the acute setting, whereas effects on cardiac repolarization and refractoriness have been more evident during long-term pharmacotherapy (Podrid, 1995). Given the results of our previous experiments (Raatikainen et al., 1996) and the data on other sodium channel blocking agents (Kus et al.,...
Although the results of the cardiac arrhythmia suppression trials (CAST Investigators, 1989; CAST II Investigators, 1992) unequivocally demonstrated that sodium channel blockers (i.e., flecainide, encainide) increase mortality in patients with recent myocardial infarction, subsequent analysis has, however, shown that class IC agents can be safely used to treat supraventricular arrhythmias in patients without structural heart disease (Hohloser and Zabel, 1992). With regard to the class I action of ATI-2001, it should also be noticed that rather than being a “pure” $I_{Na}$ blocker, ATI-2001 possesses multiple electrophysiological properties that closely mimic those of the parent molecule amiodarone. Compelling data from individual clinical trials and meta-analyses of multiple smaller trials suggest that amiodarone is also effective and safe for patients in whom class I agents have a proclivity to increase mortality (e.g., patients with recent myocardial infarction or severe heart failure) (Connolly, 1999). Whether these data can be extrapolated to ATI-2001 remains to be established.

Atrial Repolarization and Refractoriness. ATI-2001 significantly prolonged atrial repolarization and refractoriness. Similar to the effects on ventricular repolarization and refractoriness (Raatikainen et al., 1996), the effects of ATI-2001 on atrial MAPD$_{90}$ and ERP more rapidly developed and washed than those observed for an equimolar concentration of amiodarone. Likewise, a 90-min infusion period of ATI-2001 prolonged atrial MAPD$_{90}$ and ERP more rapidly at both slower (ACL = 250 ms) and faster (ACL = 200 ms) atrial-pacing rates. These findings are in agreement with previous studies that demonstrated that, unlike some other class III agents, the prototypical compound amiodarone also exerts frequency-independent effects on cardiac repolarization (Anderson et al., 1989; Huikuri and Yli-Mayry, 1992; Sager et al., 1993). Furthermore, the anticipated ability of ATI-2001 to block sodium channels in a use-dependent manner (Raatikainen et al., 1996) should further delay recovery of excitability, and thereby additionally lengthen refractoriness (i.e., postrepolarization refractoriness) as a function of atrial rate. Such a property would not only enhance the antiarrhythmic efficacy of the drug but also improve control of heart rate during supraventricular tachyarrhythmias.

Reports on the effects of acute amiodarone on atrial action potential duration have been conflicting. A moderate prolongation has been demonstrated by some investigators, but others have shown no substantial change or even shortening (Kodama et al., 1997). The observed differences can be explained at least in part by species-dependent differences in the ionic currents mediating repolarization of the action potential. In the current study, amiodarone moderately prolonged the atrial monophasic action potential. Nevertheless, the acute effects of ATI-2001 on atrial repolarization and refractoriness were significantly faster and greater than those of an equimolar concentration of amiodarone. As a result of its rapid effect on atrial repolarization, ATI-2001 may be similar to the “pure” class III agents such as ibutilide and dofetilide (Singh et al., 1999). These agents effectively convert not only atrial fibrillation but also atrial flutter to normal sinus rhythm. In contrast, class I agents (e.g., flecainide) have only a minor effect on atrial flutter despite their 70 to 80% efficacy in acute atrial fibrillation (Costeas et al., 1998).

Negative Dromotropic AV Nodal Effects

The initial pharmacotherapy of reentrant supraventricular tachyarrhythmias involving the AV node should be directed at interrupting the circuit at the level of the proximal AV node (Ganz and Friedman, 1998). The potent negative dromotropic effect of ATI-2001 is in concordance with our previous finding that the analog reduces sinoatrial rate in guinea pig spontaneously beating hearts (Raatikainen et al., 1996). Specifically, ATI-2001 appears to depress excitability and conduction in all tissues with slow (I$_{Ca}$-dependent) action potentials. In addition, the effect of the “ideal” antiarrhythmic drug should be maximal during tachycardia and minimal during slow heart rates (i.e., frequency dependent). Prolongations of the A-H interval at shorter atrial cycle lengths, the AV nodal ERP, and WCL caused by ATI-2001 indicate that the negative dromotropic effect of this drug became greater as the atrial rate increased. Consequently, ATI-2001 would be expected to terminate and/or prevent the onset of paroxysmal supraventricular tachyarrhythmias. Although the pharmacokinetic properties of ATI-2001 (i.e., significantly faster onset of action and rapid washout after cessation of the drug infusion) seem superior to amiodarone, they are unlikely to provide any advantage over adenosine or i.v. verapamil in the acute treatment of reentrant supraventricular tachyarrhythmias.

The AV node not only has an important role in the pathogenesis of paroxysmal supraventricular tachyarrhythmias but also in controlling ventricular rate during atrial tachyarrhythmias. An important physiological characteristic of AV nodal conduction is the phenomenon of frequency dependence, whereby conduction through the AV node becomes progressively slower as the atrial rate is increased (Merideth et al., 1968; Meijler et al., 1996). Drugs that exacerbate the modulatory effects of atrial rate on AV nodal conduction delay provide additional protection against excessive ventricular rate during rapid atrial fibrillation or flutter. Thus, it is important to consider that ATI-2001 may possess some advantages over the older antiarrhythmic agents in the treatment of atrial tachyarrhythmias. For example, when used to treat acute atrial flutter (and atrial fibrillation), sodium channel blockers that effectively slow atrial conduction velocity, may paradoxically accelerate ventricular rate. That is, as the atrial rate slows, the AV nodal conduction ratio may change from 2:1 to 1:1, leading to an abrupt increase in ventricular rate (Friedman and Stevenson, 1998). In contrast, the negative chronotropic (Raatikainen et al., 1996) and dromotropic effects of ATI-2001 (and amiodarone) are expected to lower ventricular rates before conversion.

Conclusions

In summary, acute ATI-2001 infusion results in multifaceted amiodarone-like effects on atrial and AV nodal electrophysiological properties. The drug suppresses excitability and conductivity in both INa- and ICa-dependent cardiac tissues, and prolongs the atrial action potential duration and refractory period. Hence, ATI-2001 should not only be useful for terminating and/or preventing atrial tachyarrhythmias, but also for treating supraventricular tachyarrhythmias in-
volving the AV node and thereby controlling ventricular response. It is also tempting to speculate that because of its more rapid washout kinetics, ATI-2001 would be less likely than amiodarone to accumulate into extracardiac tissues. Whether these properties will render ATI-2001 less hazardous than amiodarone for long-term treatment of atrial fibrillation and other supraventricular tachyarrhythmias remains to be established.

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