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Oral Vanoxerine Prevents Reinduction of Atrial Tachyarrhythmias: Preliminary Results

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Abstract

Background—Vanoxerine is a promising, new, investigational antiarrhythmic drug. The purpose of this study was to test the hypothesis that oral dosing of vanoxerine would first terminate induced atrial flutter (AFL) and atrial fibrillation (AF), and then prevent their reinduction.

Methods—In five dogs with sterile pericarditis, on the fourth day after creating the pericarditis, we performed electrophysiologic (EP) studies at baseline, measuring atrial excitability, refractoriness (AERP) and conduction time (CT) when pacing from the right atrial appendage, Bachmann's bundle (BB), and the posteroinferior left atrium at cycle lengths (CLs) of 400, 300 and 200 ms. Then, after induction of AFL or AF, all dogs received hourly oral doses of vanoxerine: 90 mg, followed by 180 mg and 270 mg. Blood was obtained to determine plasma vanoxerine concentrations at baseline, every 30 minutes, when neither AFL nor AF were inducible, and, finally, one hour after the 270 mg dose. Then we repeated the baseline EP studies.

Results—Four dogs had inducible, sustained AFL, and one dog only had induced, nonsustained AF. In four AFL episodes, oral vanoxerine terminated the AFL and then rendered it noninducible after an average of 111 minutes (range 75–180 minutes) after the first dose was administered. The mean vanoxerine plasma level at the point of noninducibility was 84 ng/ml, with a narrow range of 76–99 ng/ml. In the dog with induced, nonsustained AF, it was no longer inducible at a drug level of 75 ng/ml. Vanoxerine did not significantly: 1) prolong the AERP except at BB, and then only at the faster pacing CLs; 2) change atrial excitability thresholds; 3) prolong atrial conduction time, the PR interval, the QRS complex or the QT interval.

Conclusions—Orally administered vanoxerine effectively terminated AFL and rendered it noninducible. It also suppressed inducibility of nonsustained AF. These effects occurred at consistent plasma drug levels. Vanoxerine's insignificant or minimal effects on measured electrophysiologic parameters are consistent with little proarrhythmic risk.

Keywords

vanoxerine; atrial fibrillation; atrial flutter; cardioversion; pericarditis

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Introduction

Vanoxerine is a piperazine derivative (1-[2-[bis(4-fluorophenyl)methoxy]ethyl]-4-[3-phenylpropyl]piperazine dihydrochloride), known as a dopamine transporter antagonist. It was developed for treatment of Parkinson's disease and depression, but lacked efficacy. During a preclinical safety screen for potential clinical indications, vanoxerine was observed to be a very potent blocker of the IKr (hERG) channel. The IKr blocking effect was more potent than presently available Class III antiarrhythmics, but unlike them, vanoxerine, because of its additional sodium and L-type calcium channel blocking properties, did not prolong the action potential duration, nor did it cause the transmural dispersion of refractoriness or prolongation of the QT interval in the canine ventricular wedge preparation, indicating minimal risk for torsades de pointes.[1] This multichannel blocking property of vanoxerine was strongly frequency dependent, especially for calcium and sodium channels[1]. Finally, clinical studies of vanoxerine in healthy human volunteers showed no adverse cardiovascular effects at concentrations studied *in vitro* tests described above.[2,3] Because of the above, studies have begun to assess vanoxerine's efficacy in the treatment and prevention of cardiac arrhythmias.

Our laboratory has recently shown in the canine sterile pericarditis model that intravenous administration of vanoxerine effectively and safely terminated AF and AFL.[4] From these studies, we predicted that oral administration of vanoxerine would also effectively terminate these arrhythmias. With this study, we go a step further to see if oral administration of vanoxerine would achieve yet another important endpoint, prevention of reinduction of AFL and AF. Our hypothesis was that oral administration of vanoxerine would not only terminate these arrhythmias, but also would render them nonreinducible. In addition, because the bioavailability of vanoxerine is variable,[4,5,6] we wanted to correlate its effects with plasma levels.

Methods

Five adult mongrel dogs weighing 18–23 kg were studied. All of the studies were performed in accordance with the guidelines of the Institutional Animal Care and Use Committee, the American Heart Association on Research Animal Use, and the Public Health Service Policy on Use of Laboratory Animals.

Creation of the Canine Sterile Pericarditis Model

As previously described,[7,8] each dog first had surgery to create the sterile pericarditis model.[7] Prior to chest closure, pairs of stainless steel wire electrodes were sutured on the right atrial appendage (RAA), Bachmann's bundle (BB), the posteroinferior aspect of the left atrium (PLA), and the right ventricular (RV) apex for subsequent use in pacing and recording. Standard postoperative care was provided, including administration of antibiotics and narcotics as needed.

Studies on Postoperative Day Four

The effects of orally administered vanoxerine on selective electrophysiological parameters and on induced AFL or AF were studied in the conscious, nonsedated state. Studies were performed on postoperative day four, as induction of sustained AFL (≥ 10 minutes) is most frequent (~ 90%) on this day, and, unless an intervention is performed, the AFL usually is very longlasting.[7] Also sustained AF (≥ 5 minutes) sometimes may be induced on this day. After reproducible induction of sustained AFL (four dogs) and multiple episodes of nonsustained AF (one dog) using standard burst atrial pacing techniques,[4,8,9] each dog received hourly doses of oral vanoxerine starting at 90 mg, followed by 180 mg and then

270 mg. Once each AFL episode terminated, efforts to reinduce the AFL using the same atrial pacing technique were repeatedly attempted until the end of the study, which lasted 180 minutes in three dogs and 230 minutes in one dog. For the dog with induced, nonsustained AF, efforts to reinduce the nonsustained AF were similarly made until the end of the study, which lasted 180 minutes. To determine plasma vanoxerine concentrations, blood was obtained at baseline, every 30 minutes, at the moment when AFL and/or AF was no longer inducible, and one hour after the last dose was given. The plasma concentrations were measured by the Drug Studies Unit at the University of California San Francisco, using a method developed for the first NIDA clinical trial of vanoxerine in healthy patients. This method uses liquid chromatography and mass spectroscopy (LCMS) to detect the vanoxerine in plasma using a monofluoro vanoxerine derivative as an internal standard, and is an alternative to the liquid chromatography method[10] used in earlier clinical trials.

Also, prior to drug administration and at the end of the study, using standard techniques,[11] we performed baseline electrophysiological studies using the RAA, BB, and PLA electrodes to determine: the stimulus threshold for atrial capture, the atrial effective refractory period (AERP), and intra-atrial conduction time during pacing at cycle lengths (CLs) of 400, 300, and 200 ms from each pacing site (BB, PLA, RAA) in turn, while recording from the other two electrode sites. In addition, the PR interval, QRS complex duration and the QT interval were measured from ECG lead II during atrial pacing at a CL of 400 ms prior to drug administration and at the end of the study.

Summary statistics for AERP were generated with GraphPad Prism software, and are presented as a mean with standard deviation. Statistical significance of vanoxerine action on measured parameters was evaluated with a paired, two tailed Student t-test. A probability of ≤ 0.05 was considered significant.

Definitions

1. AFL was defined as a rapid atrial rhythm (rate > 240 bpm) characterized by a constant beat-to-beat CL, polarity, morphology, and amplitude of recorded bipolar electrograms. Sustained AFL was defined as lasting ≥ 10 minutes.
2. AF was defined as a rapid atrial rhythm characterized by continuous variability of the beat-to-beat CL, polarity, morphology, and amplitude of bipolar atrial electrograms recorded from at least 1 of the 3 atrial electrode recording sites. Sustained AF was defined as lasting ≥ 5 minutes.
3. Reproducible induction was defined as episodes of sustained AFL or AF induced by the same pacing induction protocol two or more times.

Results

Effects of Oral Administration of Vanoxerine on Induced Atrial Arrhythmias

A. AFL

1 After oral administration of vanoxerine in the four dogs with sustained AFL, the arrhythmia spontaneously terminated in all four.

2 Following administration of vanoxerine and prior to termination, each episode of AFL was associated with CL prolongation. Just before termination, beat-to-beat CL variation typically occurred. A representative example is shown in Figure 1.

3 Repetitive efforts to reinduce AFL produced short episodes of nonsustained AFL or AF until finally, neither were inducible (Figures 2 and 3). We did not

analyze the few episodes of induced AFL or AF that only lasted a few seconds. Noninducibility occurred after an average of 111 min (range 75–180 min) after the first dose was administered (Figure. 4). In this group of four dogs, two received two doses and the other two dogs received three doses of oral vanoxerine before the AFL became noninducible.

4 The mean vanoxerine plasma level at the time when AFL was no longer reinduceble was 84 ng/ml, with a relatively narrow range of 76–99 ng/ml (Figure 4), thereby identifying a “therapeutic” plasma level range.

B. AF

5 In the one dog with induced, nonsustained AF, it was no longer inducible at a vanoxerine plasma level of 75 ng/ml, i.e., within the same range as noted above for AFL.

Effects of Vanoxerine on Selected Electrophysiological Parameters

In all five dogs, vanoxerine:

1. did not significantly change the AERP at the RAA and PLA sites at any pacing CL, but significantly prolonged the AERP at the BB site at 300 and 200 ms pacing CL. Histograms of the AERP data obtained during pacing from all three pacing sites are shown in Figure 5;
2. did not significantly change atrial excitability thresholds (Table 1);
3. did not prolong the PR interval, QRS complex duration or QT interval at a pacing CL of 400 ms. QT interval values pre and post vanoxerine are presented in Figure 6; and
4. did not affect the intraatrial conduction times between any sites at any pacing CLs (400, 300, and 200 ms; data not shown).

Discussion

Main Findings

To our knowledge, this is the only study where an antiarrhythmic drug with multichannel blocking properties was acutely administered orally to study not only the effects on termination of induced atrial arrhythmias, but also, and just as important, the effects on reinduction of these arrhythmias after their termination. The main findings in this study were that oral vanoxerine not only terminated the induced atrial arrhythmias, but it also prevented their reinduction. The latter occurred over a narrow range of vanoxerine’s plasma level. The inability to reinduce any atrial arrhythmias after reaching a critical plasma level was striking in our model, in which atrial arrhythmias are usually very easily and readily inducible.[4,7,8] Additionally, the orally administered vanoxerine had no significant effects on the P-R interval, the QRS complex duration, nor the Q-T interval in the ECG. It also had no significant effects on the atrial stimulus threshold or intra-atrial conduction time. Vanoxerine did not increase the AERP except at BB, and even then, only at very short pacing CLs. The presence of Purkinje-like fibers in BB,[12] not present at the other pacing sites, may explain this latter effect of vanoxerine. As AERPs were determined at the end of the study, this effect of vanoxerine on BB may not have been present at the much lower plasma levels that prevented reinduction of AFL and AF. Vanoxerine’s effects on these ECG and electrophysiologic parameters were obtained at the end of the study, when plasma concentration levels of vanoxerine were much higher than the therapeutic concentrations. These findings suggest a very favorable therapeutic index for oral vanoxerine.

Effects of Vanoxerine on AFL and AF

In our study, vanoxerine's effects on AFL are clear, as it terminated induced AFL and rendered it nonreinducible. The fact that in our study only nonsustained AF was induced at baseline seemingly might limit interpretation of the effects of vanoxerine on prevention of reinducibility of AF after vanoxerine's oral administration. However, as is well documented in our animal model[11] and in patients,[13,14,15] induced AFL is virtually always preceded by a variable period of AF. In addition, AFL is most effectively induced in patients undergoing electrophysiological studies with atrial burst pacing.[13,16] Thus, our inability to reinduce AFL after oral vanoxerine administration legitimately can also be considered to reflect an inability to reinduce AF.

Although the onset of vanoxerine's effects had a variable time course in each dog, the plasma concentration of vanoxerine at which nonreinducibility occurred in all dogs was over a very narrow range. The differences in the onset of vanoxerine's effects on arrhythmia noninducibility can be explained by variable bioavailability of the drug. In short, despite the inter-individual oral bioavailabity differences in our dogs, a narrow vanoxerine plasma level identified the arrhythmia noninducibility threshold.

Potential Clinical Implications

Most antiarrhythmic drugs are not as effective as we would like, and all have the potential for serious adverse effects. Oral administration of an antiarrhythmic drug that has an excellent safety profile, is highly efficacious, and has a relatively rapid onset of action would be very desirable to use for the purpose of convenient, safe, and relatively quick termination of AFL and AF in patients. The data from this and our previous studies [1,4] strongly support the notion that vanoxerine should be a safe and effective oral drug to treat AFL and AF acutely, and potentially even chronically.

Use of Class I and Class III antiarrhythmics to treat AF and AFL is well recognized. However, the presence of structural heart disease, renal failure and potentially life threatening adverse effects limit their use. Amiodarone is acknowledged to be the most effective and widely used drug in suppression of AF. [17,18] Its efficacy is thought to be due to its multichannel blocking properties. However, its efficacy is mainly demonstrated after chronic administration, and it is not effective acutely for termination of AFL and AF.[20] Moreover, its prolonged use is also associated with significant risk for developing serious adverse effects,[18,19] limiting its usefulness.

Limitations

Only one dog in our study had induced AF (non-sustained) that was rendered noninducible with vanoxerine. However, as discussed above, orally administered vanoxerine should also be considered effective in preventing the reinduction of AF, as the inability to reinduce AFL indicates the inability to induce AF in our model.[14,15]

In addition, our study does not provide for a mechanistic explanation as to why vanoxerine successfully terminates atrial arrhythmias and prevents their reinduction in our model. We did not observe prolongation of the P-R interval, the QRS complex duration, nor the Q-T interval in the ECG. Vanoxerine also did not significantly change the atrial stimulus thresholds, intra-atrial conduction times and AERP. Hence, the mechanism by which vanoxerine exerts its antiarrhythmic effect remains elusive. Our previous study with intravenous vanoxerine resulted in almost identical findings.[4] The antiarrhythmic effects of vanoxerine were reproducibly observed, and yet, no change in ECG parameters, atrial stimulation thresholds or intra-atrial conduction times was detected. In our prior study of intravenous administration of vanoxerine, we did notice a prolongation of the AERP at the

BB site, albeit only at very short pacing CLs, and there was a significant prolongation of the ventricular effective refractory period (VERP).[4] Those data are very similar to the present study, except that we did not test for the VERP. At this point, we cannot provide a plausible explanation for the putative antiarrhythmic ionic mechanisms of vanoxerine without speculating. Although finding how vanoxerine works at the molecular level is both important and intriguing, our study did not address the molecular antiarrhythmic properties of vanoxerine. Future, properly designed studies to answer this specific question are needed. However, at the whole heart level, we do understand that vanoxerine terminates AFL and AF by interrupting the driver, and prevents reinduction of these arrhythmias by preventing reformation of the driver in our model.[4]

Conclusions

Vanoxerine, a drug with multichannel blocking properties, demonstrated an excellent efficacy and safety profile, as well as a relatively rapid onset of action after oral administration to terminate and prevent reinduction of AFL and AF. Its low potential for ventricular proarrhythmia is suggested by its modest effects on ventricular refractoriness, QT, and QTc intervals found in this and prior studies in an animal model [4] and in humans.[2,3] This combination of efficacy and safety demonstrated to date suggests that vanoxerine, a drug with multi-ion channel blocking effects similar to amiodarone, has the potential to become a valuable antiarrhythmic agent for the treatment of AFL and AF, and perhaps even for other arrhythmias. Further studies are needed to evaluate this potential.

Acknowledgments

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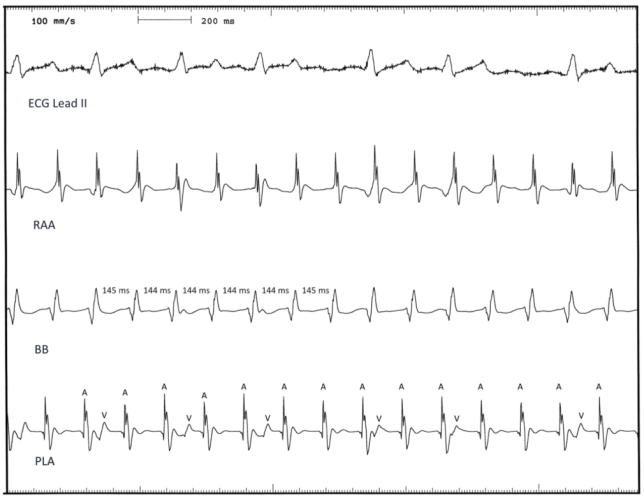

Fig.1A

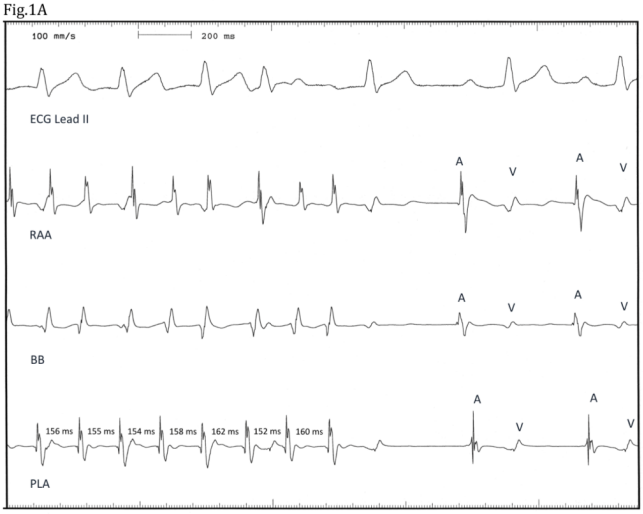

Fig.1B

Fig. 1.

Fig. 1A and 1B: ECG lead II and atrial electrograms from the RAA, BB, and PLA sites recorded simultaneously during induced, sustained AFL at a CL of 144 ms before vanoxerine administration (Panel A) and at termination of the AFL after oral administration of vanoxerine (Panel B). (Panel A): Shown is a representative example from a reinitiated AFL episode lasting 22 minutes prior to termination with vanoxerine. After the termination of this episode, AFL was no longer inducible. The AFL cycle length (CL) was 144 ms. (Panel B): Termination of AFL followed by the first two beats of sinus rhythm. Prior to termination of AFL the beat-to-beat CL became variable, but the morphology of the atrial electrograms was preserved. CLs of each beat prior to termination are indicated. The average CL of the last 10 beats was 156 ms. RAA = right atrial appendage; BB = Bachmann's bundle; PLA = posterinferior left atrium. A= atrial complex on the recorded electrogram; V= ventricular complex on the recorded electrograms. See text for discussion.

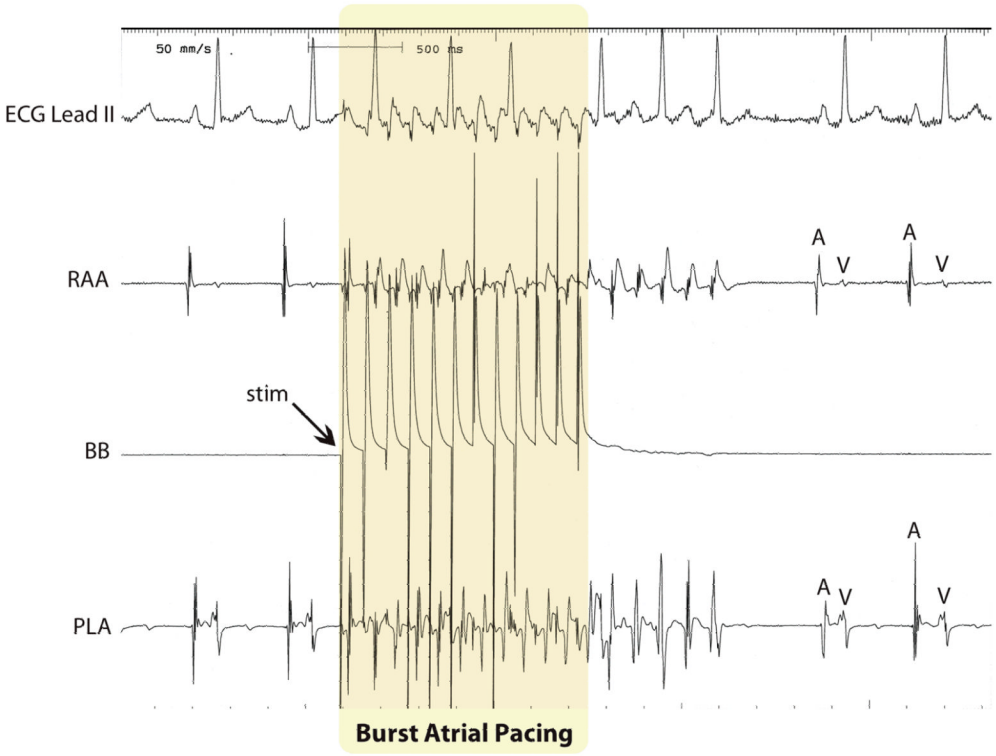

Fig. 2.

Representative example of burst atrial pacing from BB in an effort to reinduce AFL following its termination by oral vanoxerine. From top to bottom: ECG lead II, RAA = right atrial appendage; BB = Bachmann's bundle and; PLA = posteroinferior left atrium; stim = stimulus artifact; A = atrial complex in the recorded electrogram; V = ventricular complex in the recorded electrogram. See text for discussion.

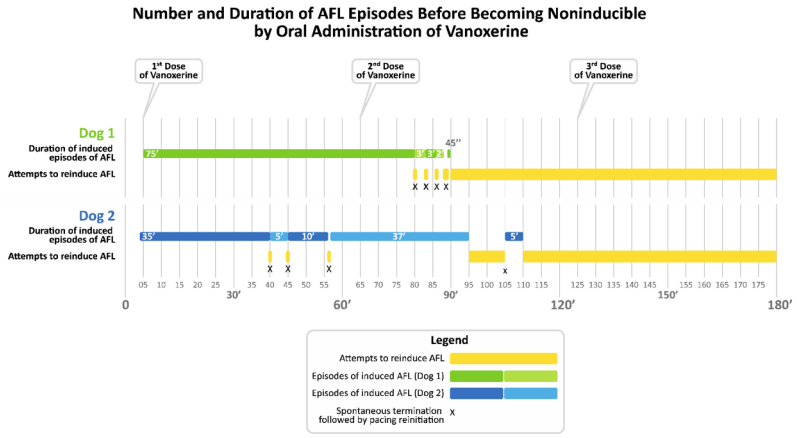

Fig. 3.

Representative examples in two dogs showing the number and duration of atrial flutter episodes after oral vanoxerine was administered. The horizontal axis represents time in minutes. Both dogs had a study that lasted 180 minutes (labeled from 0 to 180 minutes). At 0 minute oral vanoxerine was administered during a stable induced sustained episode of AFL. The duration of each AFL episode is given in minutes in each bar. For Dog #1 the first episode of AFL lasted 75 minutes and then terminated spontaneously. Immediate attempt to reinduce AFL produced much shorter episodes of AFL lasting 3 minutes, 3 minutes, 2 minutes and 45 seconds respectively. Afterwards, repetitive efforts to reinduce AFL until the end of the study were unsuccessful. Ninety minutes elapsed from the time the first dose of vanoxerine was given until the arrhythmia became noninducible. For Dog # 2 the first episode lasted 35 minutes before spontaneously terminating. Subsequent attempts to reinduce AFL produced episodes lasting 5 minutes, 10 minutes, 37 minutes and 5 minutes, respectively. Note that it took 10 minutes of repetitive attempts to reinduce the last episode of nonsustained AFL. The total time after the first dose of vanoxerine was given and AFL became noninducible was 110 minutes. This time included the duration of each AFL episode and the time spent to reinduce each episode for both dogs.

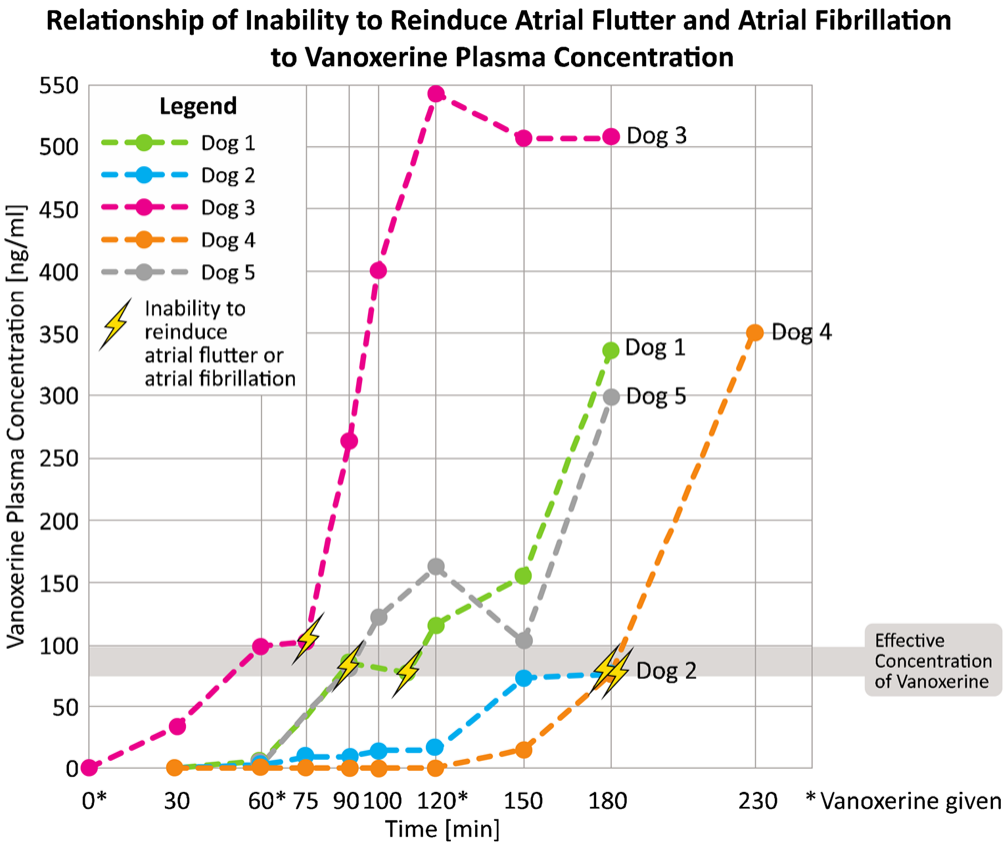

Fig. 4.

Relationship between the effective plasma concentration of vanoxerine, the time after the initial oral dose was administered, and the inability to reinduce AFL and nonsustained AF. The grey shaded area corresponds to the inability to reinitate AFL and AF. Although the time to inability to reinduce AFL or AF varied widely (75 to 180 minutes), the effective concentration of vanoxerine rendering AFL and AF nonreinducible was relatively narrow.

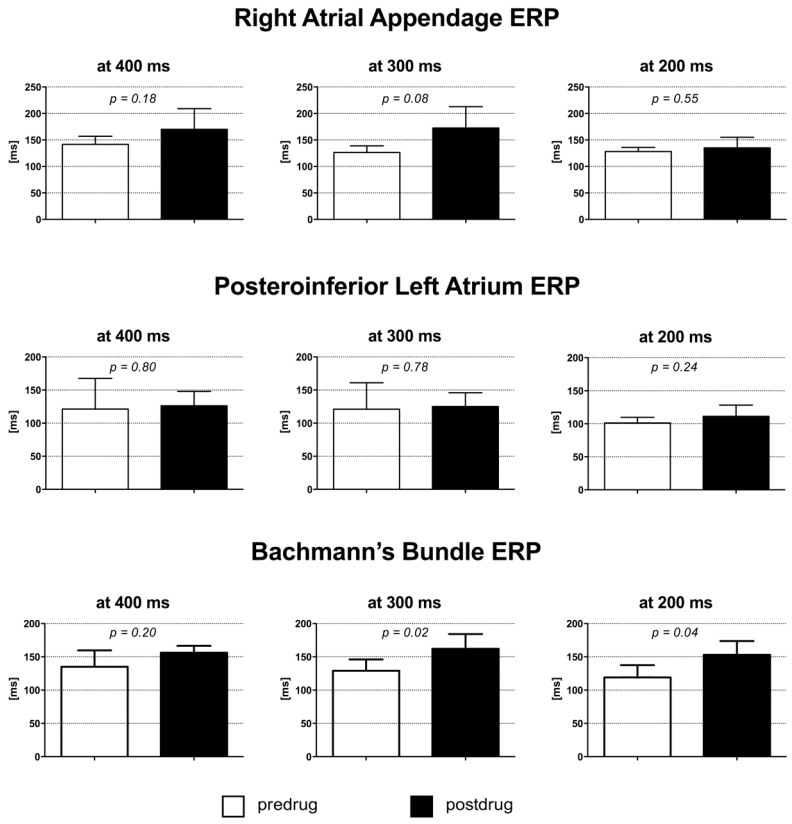

Figure 5.

Mean atrial effective refractory periods (AERPs) for all 5 dogs measured at 400, 300 and 200 ms pacing CLs at Bachmann's Bundle (BB), the posteroinferior left atrium (PLA), and the right atrial appendage (RAA). The mean AERP values in ms are provided in each individual histogram panel. Note the nonsignificant p values for AERPs measured at all pacing Cls atthe PLA and RAA. At BBshowed are nonsignificant p values for AERPs measured at the 400 ms pacing CL, but significant differences at 300 ms and 200 ms pacing CLs. See text for discussion.

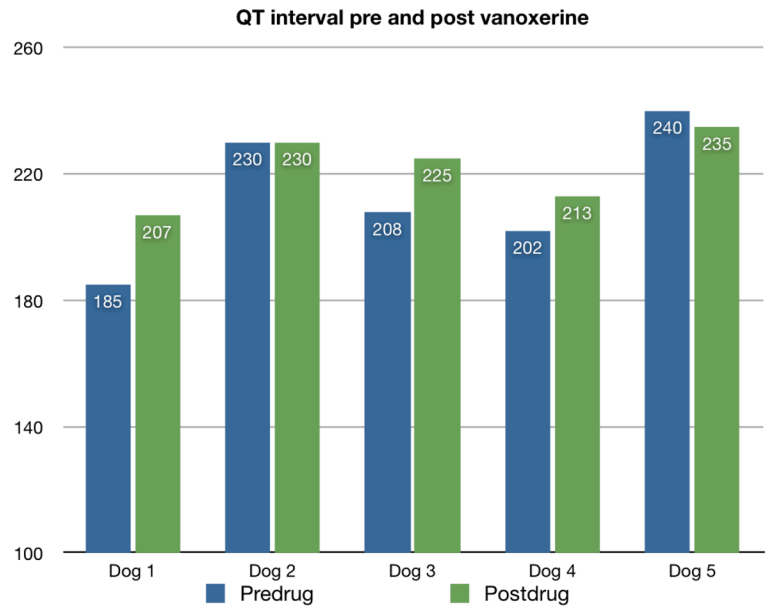

Figure 6.
QT interval values in ms in all 5 dogs pre and post vanoxerine administration during atrial pacing at 400 ms. Numerical values for each dog are presented in each bar. No significant clinical differences were observed.

Table 1

Atrial pacing thresholds from each pacing site pre and post vanoxerine administration.

CL's	Predrug (mA)	Postdrug (mA)	P Value
RAA			
400	2.5 ± 1.6	2.7 ± 2.3	0.54
300	3.0 ±1.6	3.4 ± 2.3	0.15
200	3.5 ± 2.2	4.3 ± 2.4	0.08
BB			
400	0.4 ± 0.2	0.5 ± 0.2	0.08
300	0.6 ± 0.2	0.7 ± 0.3	0.19
200	0.7 ± 0.2	0.9 ± 0.4	0.07
PLA			
400	4.9 ± 2.5	7.8 ± 6.2	0.23
300	6.3 ± 3.4	9.4 ± 6.1	0.07
200	4.5 ± 3.5	12.9 ± 12.1	0.2

Values are presented as a mean ± the standard deviation. Statistically nonsignificant differences are observed. RAA = right atrial appendage; BB = Bachmann's bundle; PLA = posteroinferior left atrium; CL's = Cycle Lengths.