Optimizing flecainide plasma concentration profile for atrial fibrillation conversion while minimizing adverse ventricular effects by rapid, low-dose intratracheal or intravenous administration☆

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ABSTRACT

Background: We investigated whether rapid administration of a low dose of flecainide, either intratracheally or intravenously (IV), could accelerate conversion of atrial fibrillation (AF) while reducing adverse ventricular effects.
Methods: Flecainide was delivered via intratracheal administration at 1.5 mg/kg bolus and compared to IV infusion at 1.0 mg/kg over 2 min (lower-dose, rapid) and 2.0 mg/kg over 10 min (ESC guideline) in closed-chest, anesthetized Yorkshire pigs. Catheters were fluoroscopically positioned in right atrium to measure atrial depolarization (P_a) duration and left ventricle (LV) to measure QRS complex duration and contractility (LV dP/dt) during atrial pacing at 140 beats/min. Flecainide was delivered intratracheally via a catheter positioned at the bifurcation of the main bronchi. AF was induced by intrapericardial administration of acetylcholine followed by burst pacing.
Results: Flecainide reduced AF duration similarly by intratracheal and IV delivery. Peak plasma levels were comparable but T_{max} differed and coincided with peaks in P_a prolongation. The area under the curve indicating sustained plasma levels was greater for higher-dose, slow IV flecainide than for either intratracheal instillation (by 32%) or lower-dose, rapid IV infusion (by 88%). As a result, higher-dose, slow IV flecainide caused 58% ($p < 0.03$) and 48% ($p < 0.006$) greater increases in QRS complex duration and 61% and 96% (both, $p < 0.02$) greater reductions in contractility compared to intratracheal and lower-dose, rapid IV flecainide, respectively.
Conclusion: Lower-dose, rapid flecainide, delivered either intratracheally or IV, optimizes the plasma concentration profile for effective conversion of AF while minimizing adverse effects on QRS complex duration and LV contractility.

1. Introduction

In the absence of structural heart disease or hemodynamic instability, intravenous (IV) flecainide (Class IA recommendation) or pill-in-the-pocket (PIP) flecainide (Class IIB recommendation) have been successfully employed to convert recent-onset atrial fibrillation (AF) [1]. The advantage of the PIP approach is that in certain patients it can be self-administered out-of-hospital immediately as needed, thereby reducing visits to the emergency department and hospitalization. The experience with PIP-antiarrhythmic drug (PIP-AAD) spans more than a decade and the overall results have generally been favorable [2–5]. However, an important limitation of PIP-AAD is the relatively long latency of effect, on the order of hours, associated with high-dose oral administration [1,6].

These considerations have prompted evaluation of a new approach for rapidly increasing antiarrhythmic drug plasma concentrations, namely, pulmonary delivery. The basic rationale is that lung administration of antiarrhythmic drugs benefits from the large surface area of alveoli, i.e., 100 m^2, which can efficiently absorb fluid, particularly in the aerosolized state. The net effect is a rapid, transient peak in drug concentration in the pulmonary venous circulation, with rapid transfer of the agent to the left atrial chamber and subsequently to the coronary arteries through the capillary network to reach the atrial myocardium and

pulmonary vein sleeves, critical structures in the initiation and maintenance of AF.

Recently, it has been shown in normal human subjects that administration of flecainide using a hand-held breath-actuated nebulizer is safe and relatively devoid of side effects while eliciting characteristic electrophysiologic changes such as lengthening of the PR interval and QRS complex duration [7,8]. In large animal models including canines and porcines, intratracheal administration of flecainide has been shown to accelerate conversion of AF [9,10].

The main goals of the present study are to compare the relative efficacy of intratracheal delivery of flecainide (1.5 mg/kg bolus) to convert AF to normal sinus rhythm to that achieved with lower-dose (1-mg/kg), rapid (2-min) and the standard higher-dose (2-mg/kg), slow (10-min) IV infusions. We tested the hypothesis that rapid delivery of lower doses of flecainide would be effective not only in converting AF to sinus rhythm but would also reduce the adverse left ventricular (LV) inotropic effects and QRS complex prolongation due to abbreviated exposure of ventricular tissue to the agent, as a result of its rapid, transient delivery via the lung route. We also postulated that by shortening the delivery time, the critical variable, atrial depolarization (P_a) duration, an indicator of intra-atrial conduction that is highly correlated ($r^2 = 0.87$, $p = 0.03$) with the conversion of AF [10], would be optimally affected. These actions would facilitate AF conversion while reducing adverse ventricular effects.

2. Methods

2.1. Experimental preparation

This study conformed to the National Institutes of Health Guide for the Care and Use of Laboratory Animals as well as to the Declaration of Helsinki. The protocol was approved by the institutional animal use committee of Beth Israel Deaconess Medical Center (Boston MA). The studies were carried out in male Yorkshire pigs weighing 36 ± 2.3 kg. The pigs were preanesthetized with telazol (4.7 mg/kg, intramuscular) and subsequently were further anesthetized using alpha-chloralose (80-mg/kg IV bolus followed by 24-mg/kg/h continuous IV infusion). The pigs were intubated and ventilated at a constant rate of 12 breaths/min and tidal volume of 400 ml per stroke.

All catheters were positioned under fluoroscopic guidance. Electrograms were obtained from a decapolar electrode catheter positioned in the LV. Mean arterial pressure (MAP) was continuously monitored from a femoral arterial sheath. LV blood pressure was continuously monitored from a pigtail catheter. A catheter was positioned in the pericardial space through the right atrial appendage for delivery of intrapericardial acetylcholine. Atrial pacing at 140 beats/min was achieved by delivering electrical stimuli via the right atrial catheter electrodes. Electrograms were recorded using a Prucka CardioLab workstation (GE Medical Systems, Milwaukee WI) from atrial and ventricular sites. For intratracheal instillation of flecainide acetate solution, a 5 Fr angiography catheter was introduced into the trachea via the endotracheal tube, extending ~1 cm past the tube, and its tip was positioned under fluoroscopy at the tracheal carina level.

2.2. Reagents and chemical analysis

Flecainide acetate dosing solutions of 1.5 mg/kg for intratracheal and of 1.0 and 2.0 mg/kg for IV delivery were prepared by dilution of premade solutions of 35 mg/ml in sterile water. Plasma samples were analyzed using a high-performance liquid chromatography tandem mass spectrometric assay at Climax Laboratories, Inc. (San Jose CA).

2.3. Study protocols

In the 30-min analysis protocol, flecainide was delivered either via intratracheal instillation or IV infusion and electrocardiographic measurements of P_a duration, QRS complex duration, LV dP/dt and MAP were obtained at 0, 2, 5, 10, 15 and 30 min during atrial pacing at 140 beats/min. In the AF protocol, the arrhythmia was induced by injection of acetylcholine (1 ml of 102.5 mM solution) into the pericardial sac followed by burst pacing at 400 beats/min for 1 min after the injection. Lavage of the pericardium with saline was performed after the start of AF to prevent further acetylcholine action. After 2 min of AF, flecainide was delivered. AF duration was compared among the flecainide and control experiments starting at 2 min after AF initiation.

In the intratracheal instillation experiments, flecainide (2 ml of 1.5 mg/kg concentration followed by 3 ml of air in a 5 cm^3 syringe) was administered in a single "push" via the modified angiography catheter positioned in the endotracheal tube at the beginning of the inspiration phase. The intratracheal dose of 1.5 mg/kg was selected based on the assumption of 75% lung bioavailability during oral inhalation of flecainide [8], which would be equivalent to a dose of 1.1 mg/kg IV, somewhat lower than the common clinical doses of 1.5 and 2.0 mg/kg given over 10 min [1]. In the IV administration experiments, flecainide (20 ml of 1 or 2 mg/kg concentration over 2 or 10 min, respectively) was infused at a constant rate via a 7 Fr sheath inserted into the right femoral vein using a syringe pump. When more than one dose of flecainide was tested in a single experiment, a washout period of 30 to 60 min was allowed between administrations in order to keep residual levels of flecainide to a minimum before testing the new dose. Sterile water was used as a placebo solution for intratracheal instillation in six experiments.

2.4. Plasma samples

Blood samples were drawn from a 7 Fr sheath placed in the jugular vein and through the LV pigtail catheter into sodium heparin tubes at 0, 2, 5, 10, 15 and 30 min after the start of IV or intratracheal flecainide administration in the 30-min analysis protocol. In the AF protocol, the blood samples were drawn through the same sheaths at the same time points until the AF terminated, when the final blood sample was drawn. All the samples were centrifuged and frozen at -80 °C.

2.5. Statistical analysis

Statistical analyses were performed using the SAS system (version 9.4) to apply ANOVA with post-hoc Dunnett's test for each time point. Data are reported as means $\pm$ SEM. Statistical significance was assumed at $p < 0.05$.

3. Results

3.1. Relationship between flecainide plasma concentration profile and atrial depolarization duration

The peak plasma levels of flecainide (C_{max}) among the groups with intratracheal 1.5 mg/kg instillation (N = 6) and the two IV doses (N = 6) were comparable, but the timing (T_{max}) differed. The C_{max}, T_{max}, and area under the curve (AUC) of sustained plasma levels for the intratracheal instillation and the two IV doses are summarized in Fig. 1 and Supplement Table 1. The AUC for the higher-dose, slow IV infusion flecainide was 32% greater than the AUC for intratracheal flecainide ($p < 0.07$) and 88% greater than the AUC for the lower-dose, rapid IV infusion ($p < 0.0003$).

There was a close relationship between the plasma flecainide concentration and the effects on atrial depolarization (P_a) prolongation (Fig. 1, left and right panels; Supplement Table 2). Intratracheal instillation of 1.5 mg/kg flecainide caused a $26 \pm 5\%$ increase in P_a duration ($p < 0.002$) at the 2-min peak effect compared to no-drug baseline. Lower-dose, rapid IV flecainide infusion resulted in a comparable $26 \pm 5\%$ increase in P_a duration ($p < 0.0001$) at the 2-min peak effect compared to no-drug baseline. The higher-dose, slow IV infusion caused a $28 \pm$
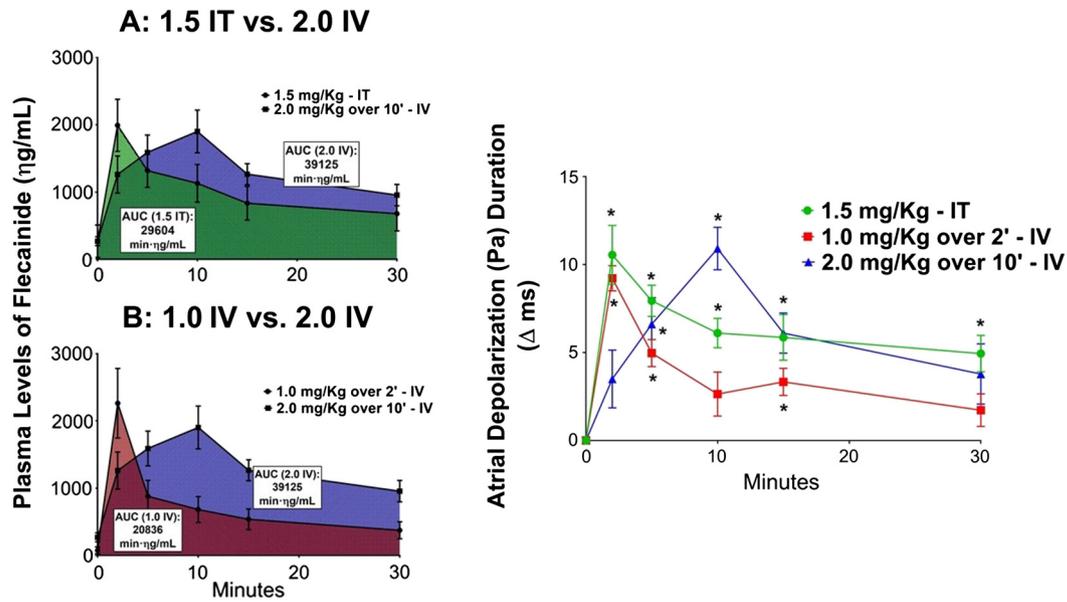
Fig. 1. Left panels: Timecourse of areas under the curve (AUC) for flecainide plasma levels following intratracheal (IT) instillation of 1.5 mg/kg bolus (N = 6) (green area) vs. 2.0 mg/kg IV infusion over 10 min (blue area) (upper panel) as well as 1.0 mg/kg IV over 2 min (red area) vs. 2.0 mg/kg IV infusion over 10 min (lower panel) (N = 6). The AUC is highest following the higher-dose, slow infusion. Each data point was calculated as mean ± SEM. Right panel: Timecourse of changes in atrial depolarization (ΔP_a) duration after administration of flecainide via intratracheal (IT) instillation of 1.5 mg/kg bolus (N = 6) (green filled circles), 1.0 mg/kg IV over 2 min (red filled squares), and 2.0 mg/kg IV infusion over 10 min (blue filled triangles) (N = 6) compared to no-drug baseline. Note the similar peak effects in P_a prolongation achieved by the 3 modes of instillation. Each data point was calculated as mean ± SEM. Significant comparisons to baseline using post-hoc Dunnett's test are represented by the asterisk ($p < 0.05$).

5% increase in P_a duration ($p < 0.0003$) at the 10-min peak effect compared to no-drug baseline. The peak effects on P_a duration did not differ significantly from each other in magnitude, but the timing of the P_a peaks coincided with the T_{max}, which occurred at 2, 2, and 10 min, respectively, i.e., at the sampling time points nearest to the completion of drug administration.

3.2. Effects on QRS complex duration

The effects of flecainide delivery on QRS complex duration also followed the plasma concentration profile. Intratracheal instillation of 1.5 mg/kg flecainide caused a 31 ± 8% increase in QRS complex duration ($p < 0.02$) at the 2-min peak effect (Fig. 2; Supplement Table 3) compared to no-drug baseline. There was no significant difference compared to the lower-dose, rapid IV flecainide, which increased QRS complex duration by 33 ± 8% ($p < 0.0002$) at the 2-min peak effect.
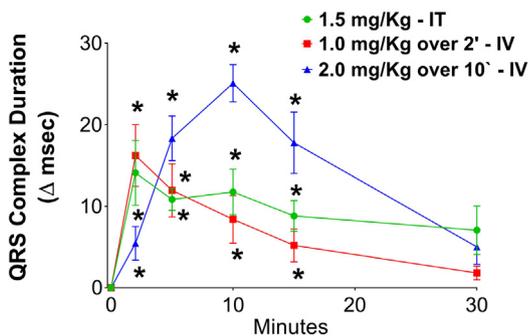
Fig. 2. Timecourse of changes in ventricular depolarization (ΔQRS) duration after administration of flecainide via intratracheal (IT) instillation of 1.5 mg/kg bolus (green filled circles) (N = 6), 1.0 mg/kg IV infusion over 2 min (red filled squares), and 2.0 mg/kg IV infusion over 10 min (blue filled triangles) (N = 6) compared to pre-drug baseline. The higher-dose, slow infusion lengthens QRS complex duration more than intratracheal 1.5 mg/kg instillation and the lower-dose, rapid IV infusion. Each data point was calculated as mean ± SEM. Significant comparisons to baseline using post-hoc Dunnett's test are represented by the asterisk ($p < 0.05$).

Higher-dose, slow IV flecainide resulted in a 1.5-fold greater increase ($p < 0.006$) in QRS complex duration of 49 ± 5% ($p < 0.0002$), which occurred later, at the 10-min peak effect.
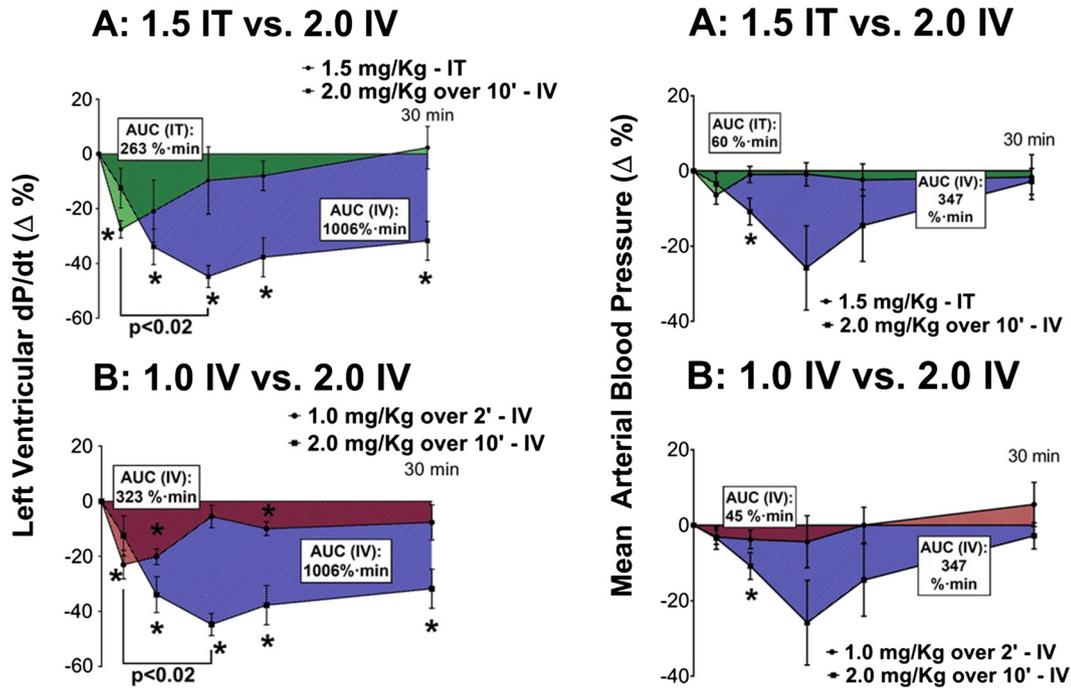
3.3. Effects on left ventricular contractility and mean arterial pressure

Effects of flecainide on LV contractility also followed the timecourse of the plasma flecainide concentration. Intratracheal instillation of 1.5 mg/kg flecainide decreased contractility (LV dP/dt) by 28 ± 3% ($p < 0.0004$) at 2-min nadir, which returned to baseline at 30 min ($p = 0.78$) (Fig. 3, left panels; Supplement Table 4) compared to no-drug baseline. Similarly, lower-dose, rapid IV infusion reduced LV dP/dt by 23 ± 5% ($p < 0.007$) at the 2-min nadir, which returned to baseline at 30 min ($p = 0.285$). By comparison, the higher-dose, slow IV infusion resulted in a 2.0-fold reduction ($p < 0.02$) in LV dP/dt of 45 ± 4% ($p = 0.0001$) at 10-min nadir and remained significantly depressed by 32 ± 7% ($p < 0.007$) at 30 min. The maximum reduction in LV dP/dt following higher-dose IV administration was 1.6-fold ($p < 0.02$) the maximum reduction following the intratracheal instillation of 1.5 mg/kg flecainide, with 3.8-fold ($p = 0.04$) reduction in the AUC (263 vs. 1006%·min) (Supplement Tables 1, 4). Furthermore, the higher-dose IV flecainide caused a 3.1-fold decrease in the AUC (323 vs. 1006%·min, $p < 0.02$) compared to the lower-dose, rapid IV infusion.

There were no significant changes in MAP for any of the flecainide dosages compared to no-drug baseline (Fig. 3, right panels; Supplement Table 5).

3.4. Atrial fibrillation duration

Intratracheal instillation of 1.5 mg/kg flecainide (N = 6) caused a 73% decrease in AF duration (from 11.1 ± 1.9 to 3.0 ± 0.5 min) compared to no-drug baseline (Fig. 4, $p < 0.005$, Supplement Table 6). This effect was similar ($p = 0.76$) to that of lower-dose, rapid IV flecainide, which reduced AF duration by 71% (from 9.3 ± 0.8 to 2.7 ± 0.8 min, $p < 0.0006$), and to that of the higher-dose, slow IV administration ($p = 0.38$), which decreased AF duration by 58% (from 9.3 ± 0.8 to 4.0 ± 0.9 min, $p < 0.003$) (N = 5). The lower-dose, rapid IV infusion reduced AF duration to a greater extent than higher-dose, slow IV infusion ($p < 0.005$).

Fig. 3. Left panels: Timecourse of the areas under the curve (AUC) of the percentage change in left ventricular (LV) contractility (∆% LV dP/dt) for intratracheal instillation of 1.5 mg/kg bolus of flecainide (green area) (N = 6) vs. 2.0 mg/kg IV infusion over 10 min (blue area) (upper panel) and for 1.0 mg/kg IV over 2 min (red area) vs. 2.0 mg/kg IV infusion over 10 min (lower panel) (N = 6) compared to pre-drug baseline. The reduction in LV contractility by the higher-dose, slow IV infusion is 3.4- to 3.8-fold that of the intratracheal 1.5 mg/kg instillation and the lower-dose, rapid IV infusion, respectively, which have similar effects. Each data point was calculated as mean ± SEM. Significant comparisons to baseline using post-hoc Dunnett's test are represented by the asterisk ($p < 0.05$). Brackets represent comparisons among the peaks. Right panels: Timecourse of the AUC of the percentage change in mean arterial pressure (∆% MAP) for intratracheal instillation of 1.5 mg/kg bolus of flecainide (green area) (N = 6) vs. 2.0 mg/kg IV infusion over 10 min (blue area) (upper panel) and for 1.0 mg/kg IV over 2 min (red area) vs. 2.0 mg/kg IV infusion over 10 min (lower panel) (N = 6) compared to no-drug baseline. Each data point was calculated as mean ± SEM. Significant comparisons to baseline using post-hoc Dunnett's test are represented by the asterisk ($p < 0.05$).

4. Discussion

4.1. Main findings

This study provides preclinical evidence confirming that rapid delivery of flecainide at lower doses is effective in accelerating conversion of AF to normal sinus rhythm with lower net delivery of drug, while reducing depression of LV contractility and QRS complex prolongation.
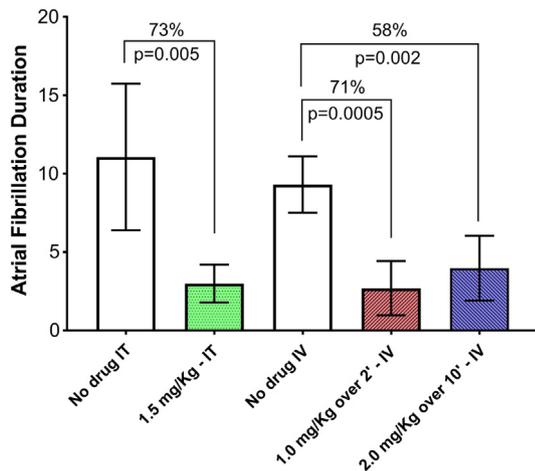
Fig. 4. Duration of atrial fibrillation (AF) in the absence of drug and following 1.5 mg/kg bolus intratracheal instillation, 1.0 mg/kg IV infusion over 2 min, and 2.0 mg/kg IV infusion over 10 min of flecainide (n = 11). The reductions in AF duration were 73%, 71%, and 58%, respectively, compared to placebo. The lower-dose, rapid IV infusion reduced AF duration to a greater extent than the higher-dose, slow IV infusion ($p = 0.005$). Values are represented as means ± SEM.

Intratracheal delivery of a rapid bolus of 1.5 mg/kg flecainide resulted in an equivalent reduction in AF duration as the standard IV dose of 2.0 mg/kg infused over 10 min, with a significantly lessened negative impact on LV inotropy and QRS complex duration. Increasing the IV infusion rate to deliver the drug in 2 rather than 10 min and administering half of the flecainide dose, i.e., 1.0 mg/kg, yielded the same magnitude of shortening in AF duration. The likely basis for the advantageous anti-AF effects of a lower-dose, rapid infusion by either intratracheal or IV administration is the abrupt peak effect of the drug on P_a duration, indicative of a rapid effect on intra-atrial conduction, and the reduced flecainide plasma concentration, which can adversely affect QRS complex duration and LV contractility (Fig. 1).

4.2. Prior studies

The experience with pulmonary delivery of antiarrhythmic drugs is limited. A key first step has been to establish safety in human subjects. A study of six healthy subjects who randomly received a 2.0 mg/kg flecainide IV infusion over 10 min or inhaled flecainide over 4 ± 1 min using a hand-held breath-actuated nebulizer revealed that inhaled flecainide was safe and well-tolerated and that this route of administration could deliver sufficient levels of the drug into the systemic circulation within 1 min to elicit QRS complex prolongation, flecainide's signature ECG effect [7,8]. The pharmacokinetic and QRS complex duration changes were also characterized in 34 healthy subjects who were given inhaled flecainide or 20, 40, or 60 mg/kg IV doses of flecainide. Inhaled flecainide was found to prolong the QRS complex in a concentration-dependent manner [7,8].

Given these encouraging results, two preclinical studies of inhaled flecainide were performed. The first study showed in a vagally induced AF canine model that intratracheal instillation of flecainide could rapidly terminate AF [9]. In a more detailed study using the current AF

model of intrapericardial acetylcholine followed by burst pacing, intratracheal instillation of flecainide was found to reduce AF duration in a dose-dependent manner [10]. Importantly, flecainide's shortening of AF duration was inversely correlated ($r^2 = 0.87$, $p = 0.03$) with its increase in P_a duration, indicating slowing of intra-atrial conduction, consistent with inhibition of peak sodium current. Flecainide exhibited a strong use-dependent effect on P_a duration, with greater prolongation present at increasing right atrial pacing rates, which favors its efficacy in suppressing fast rhythms such as AF [11]. However, the effects of intratracheal flecainide in decreasing AF duration were not compared to IV administration, which is the focus of the current study.

4.3. Present study

The current investigation demonstrated that the rate of delivery of flecainide for both the intratracheal and IV routes of administration is critical to their anti-AF effects. The more rapid was the delivery, the greater was the separation between atrial and ventricular effects. Specifically, rapid delivery pharmacokinetics favored improved AF conversion while limiting adverse effects, including depression of LV contractility and QRS complex prolongation, which are associated with proarrhythmia, especially in the presence of ischemic heart disease and heart failure. Bolus intratracheal instillation of flecainide is inherently suited for the pharmacokinetic profile of a rapid peak and subsequent rapid dissipation. Intratracheal instillation of flecainide was as effective as the standard IV infusion of 2 mg/kg over 10 min in reducing AF duration with relatively low plasma flecainide levels (Figs. 1, 4). Using a rapid delivery protocol, the IV dose of flecainide, reduced by 50% to 1 mg/kg, decreased AF duration and reduced flecainide plasma concentration. Both intratracheal and lower-dose IV flecainide attenuated the agent's effects on QRS complex prolongation and LV inotropy (Figs. 2, 3).

The precise mechanisms whereby intratracheal instillation of flecainide results in abrupt conversion of AF to normal sinus rhythm remain to be determined. Flecainide can reduce reentrant activity by depressing the slope of action potential duration restitution and dispersion of repolarization, culminating in suppression of wavebreak [12].

4.4. Limitations

The main limitation is the use of a non-human species. However, the porcine model is widely used in cardiac electrophysiologic studies of the ventricle in response to myocardial ischemia and infarction and has generally been found to be relevant [13]. The intact pig model has been less widely used in AF conversion studies but results from this [10,14] and other laboratories [15–17] appear to provide useful insights. The changes in QRS complex duration found in this and a prior detailed preclinical pharmacokinetic study [18] revealed a comparable relationship between intratracheal instillation of flecainide, plasma concentration levels, and effects on PR interval and QRS complex duration similarly to normal human subjects undergoing testing with a hand-held nebulizer [7,8].

4.5. Conclusion

The present study demonstrates that lower-dose flecainide, rapidly delivered via either intratracheal instillation or IV infusion, can effectively convert AF to normal sinus rhythm. This effect occurs with significantly less depression of LV contractility and QRS complex prolongation when compared to the higher standard IV dose administered at the slower infusion rate [1]. The physiological basis for minimizing the potentially deleterious ventricular effects of flecainide appears to be related to a first-pass bolus to the left atrium. Pulmonary delivery produced rapid increases in peak plasma concentrations of flecainide

that coincided with increases in P_a duration, a parameter that is inversely correlated with AF duration [10]. The benefits of pulmonary delivery, which include optimizing separation of anti-AF actions from adverse ventricular effects, deserve evaluation with respect to other antiarrhythmic drugs and include the opportunity for out-of-hospital self-administration using an inhaler.

Conflict of interests

Messrs. Marum, Bortolotto, de Antonio, and A. Silva, Ms. B. Silva, and Dr. Verrier have no conflicts of interest relevant to the study. Dr. Belardinelli is an employee of InCarda Therapeutics, Inc.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2018.09.029.

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