Comparative Pharmacokinetic and Electrocardiographic Effects of Intratracheal and Intravenous Administration of Flecainide in Anesthetized Pigs

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Abstract: We compared the pharmacokinetic (PK) profile and electrocardiographic (ECG) changes in response to intratracheal instillation of flecainide acetate into the left atrium and ventricle with intravenous (IV) flecainide acetate administration. In 12 closed-chest anesthetized Yorkshire pigs, we monitored the QRS complex and PR, JT_c, and QT_c intervals during sinus rhythm and correlated changes with venous plasma drug concentrations before and at 2, 5, 10, 15, and 30 minutes after drug administration. Intratracheal instillation of flecainide (0.75 and 1.5 mg/kg, rapid bolus) caused dose/concentration-dependent increases in the QRS complex duration of 10% and 19%, respectively, at 2 minutes, coinciding with peak venous plasma levels (1688 ± 177 and 2808 ± 217 ng/mL, respectively). IV infusion of flecainide (2 mg/kg) over 2 or 10 minutes similarly prolonged QRS complexes and PR intervals (both, $P < 0.001$). Intratracheal flecainide instillation increased PR interval briefly at 5 minutes. Neither intratracheal nor IV flecainide affected JT_c or QT_c intervals. Thus, the PK pattern of intratracheal instillation of flecainide is comparable to IV administration, although the absolute plasma concentrations were higher with IV infusion. Both modes of delivery elicited ECG changes that were consistent with the expected pharmacological activity of flecainide.

Key Words: inhalation, flecainide, atrial fibrillation, pharmacokinetics, pulmonary delivery

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INTRODUCTION

Atrial fibrillation (AF) is a prevalent condition, affecting ~5.2 million individuals in the United States.[1] Among the 4 types of AF, paroxysmal AF (PAF) is common and is often associated with disabling symptoms that adversely affect quality of life and increase the risk of stroke and other cardiovascular diseases such as heart failure.[2] Chronic oral medical therapies are limited to an efficacy of ~50% in suppressing recurrences of PAF.[3]

Patients with PAF and intermittent episodes (between once a month to once a year) of AF are increasingly being managed with the so-called "pill-in-the-pocket" regimen for self-led cardioversion.[4,5] Without the "pill in the pocket" regimen, they often require a visit to the emergency department for cardioversion. Several investigators have tested the potential efficacy of the class IC antiarrhythmic agents flecainide or propafenone in a single self-administered oral loading dose (eg, ~300 mg of flecainide), outside of the hospital, for conversion of AF to sinus rhythm without the need for assistance from medical staff or chronic medication with antiarrhythmic drugs.[6]

Alboni et al[4] studied 165 patients who took class IC agents orally according to the pill-in-the-pocket approach and found that the rate of adverse effects was low, with only 1 case of atrial flutter with rapid conduction. Importantly, there was a substantial decrease in emergency department visits and hospital admissions.[4] Murdock et al[7] reported that the "pill in the pocket" approach with ranolazine, an agent that has as its main action inhibition of cardiac late I_{Na} but also inhibition of peak I_{Na} and I_{Kr},[8] was also safe and effective. In a recent systematic study of "pill in the pocket" administration of class IC antiarrhythmic drugs (PIP-AAD), Andrade et al[9] found, although this approach can be effective in selected patients (eg, up to 77%), that a number of clinical factors, such as lack of efficacy and hypotension, and other adverse events, such as conversion to atrial flutter necessitating electrical cardioversion and syncopal conversion pauses, limits widespread application of the PIP approach with either flecainide or propafenone. Another limitation of the "pill in the pocket" approach is the relatively long time required to reach peak plasma levels (C_{max}); the T_{max} has been reported to be 2.3 ± 0.7 hours.[10]

The question arises as to whether yet more convenient and efficient means of delivering antiarrhythmic agents both in- and out-of-hospital to critical arrhythmogenic structures might be feasible. Pulmonary delivery potentially through oral inhalation offers a number of inherent advantages. Specifically, the pulmonary airways efficiently absorb agents in solution, especially when aerosolized, resulting in a rapid

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peak drug concentration in the systemic circulation. The drug is transported by first pass directly to the left atrium via the pulmonary veins, where critical structures in the initiation and maintenance of AF are present, eg, pulmonary vein sleeves. It is important to recognize that not all of the drug will be absorbed into the alveoli as a portion may be absorbed in the bronchi or remain in the lungs.

The main goal of this study was to compare the pharmacokinetic (PK) and pharmacodynamic (PD) effects of intratracheal instillation of the class IC agent flecainide with those of intravenous (IV) infusion at both slow and rapid rates during sinus rhythm. An extensive series of electrocardiographic and hemodynamic parameters was assessed. We also compared the relative plasma concentrations achieved in the left ventricular chamber and systemic circulation with intratracheal versus IV administration. We hypothesized that intratracheal instillation would generate peak plasma concentrations similar to a rapid IV infusion of the same drug as a consequence of pulmonary vein delivery and would thus generate comparable electrocardiographic effects without inducing ventricular arrhythmias or bradycardia. Flecainide was selected because of its widespread use and promising evidence regarding its effect of converting AF to sinus rhythm using the "pill in the pocket" regimen.[4,6]

METHODS

Experimental Preparation

This study conformed to the Position of the American Heart Association on Research Animal Use, as well as to the Declaration of Helsinki. The protocol was approved by the institutional animal care and use committee of Beth Israel Deaconess Medical Center. The studies were conducted in male Yorkshire pigs (N = 12) weighing 36 ± 1.0 kg (mean ± SEM). The pigs were preanesthetized with telazol (4.7 mg/kg, intramuscular) and subsequently further anesthetized using alpha-chloralose (80 mg/kg, IV bolus, followed by 24 mg/kg/h continuous IV infusion). During the surgical intervention, the animals were further anesthetized using 1% isoflurane. 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 (Fig. 1). Ventricular electrograms were obtained from a decapolar electrode catheter positioned in the left ventricles (LV). Arterial blood pressure was continuously monitored from a femoral arterial sheath. 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 5Fr 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 (Fig. 1).

Reagents

Flecainide acetate dosing solutions of 0.75 and 1.5 mg/kg for intratracheal delivery and 2.0 mg/kg for IV delivery were prepared by dilution of premade solutions of 30 or 35 mg/mL in sterile water.

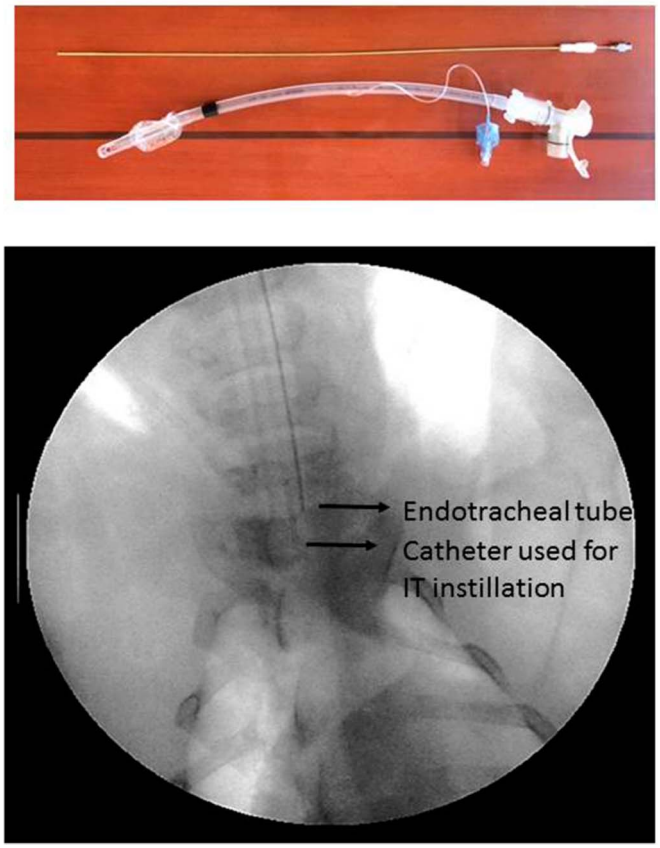

FIGURE 1. Upper panel shows components of the intratracheal delivery system including a 5Fr angiography catheter with a Y adapter with a side hole to permit introduction of the 9Fr catheter into the endotracheal tube. Lower panel: fluoroscopic image of the experimental setup for intratracheal instillation of flecainide. A modified angiography catheter is positioned inside the endotracheal tube proximal to the bronchial bifurcation. The catheter extends ~1 cm past the end of the endotracheal tube to allow complete distribution of the flecainide bolus.

Study Protocol

In the IV administration experiments, flecainide (20 mL of 2 mg/kg concentration) was infused over 2 or 10 minutes via a 7Fr sheath inserted into the right femoral vein. In the intratracheal instillation experiments, flecainide (2 mL of 0.75 mg/kg or 1.5 mg/kg concentrations, followed by 3 mL of air in a 5-cc syringe) was administered in a single "push" via the modified angiography catheter positioned in the endotracheal tube at the beginning of the inspiration phase. When more than 1 dose was tested in a single experiment, a washout period of 30–60 minutes was allowed to keep residual levels of flecainide to a minimum before testing the new dose. In the experiments with intratracheal delivery, the 0.75-mg/kg dose was always given before the 1.5-mg/kg dose. In the experiments with 2.0-mg/kg IV infusion over 2 minutes, the drug was given

without prior intratracheal delivery (N = 4) or after prior intratracheal flecainide delivery (N = 3). In no case did the baseline plasma levels at 60 minutes after the end of delivery differ significantly from the no-drug reference. Electrocardiographic measurements of the QRS complex and PR, JT_c, and QT_c intervals were performed at 0, 2, 5, 10, 15, and 30 minutes during sinus rhythm. The JT and QT intervals were corrected using Bazett's formula. Saline was used as a placebo solution for intratracheal instillation in 3 experiments to determine any possible cardiovascular effects of the intratracheal instillation procedure per se.

Plasma Samples

Blood samples were drawn from a 7Fr sheath in the jugular vein and through the LV pigtail catheter into sodium heparin tubes at 0, 2, 5, 10, 15, and 30 minutes after the start of IV or intratracheal flecainide. The samples were centrifuged and frozen at −80°C until drug level determination was performed using a high-performance liquid chromatography tandem mass spectrometry assay at Climax Laboratories, Inc. (San Jose, CA).

Statistical Analysis

Statistical analyses were performed using the SAS system (version 9.4) to apply analysis of variance (ANOVA) with post hoc Dunnett's test for each time point. Linear regression was applied to determine the correlation of ECG changes with flecainide plasma concentrations. Data are reported as mean values ± SEM. Statistical significance was assumed at $P < 0.05$.

RESULTS

Pharmacokinetic Responses

After rapid IV infusion of flecainide (2 mg/kg over 2 minutes), both LV and venous plasma levels achieved maximum concentration (C_{max}) at 2 minutes ($P < 0.05$ for both compared with predrug baseline) and progressively declined throughout the 30-minute experiment to baseline levels (Fig. 2). Slow IV infusion of flecainide (2 mg/kg over 10 minutes) revealed a different PK pattern compared with rapid IV infusion, and the absolute plasma concentrations were higher after the 2-minute IV infusion. During the 10-minute IV infusion, plasma levels of flecainide increased slowly, achieving a C_{max} at 10 minutes (LV: $P = 0.02$; venous: $P = 0.01$) and decreased by 30 minutes.

Both the 1.5 mg/kg and 0.75 mg/kg doses of flecainide, when delivered over 2 minutes by intratracheal instillation, revealed a PK pattern similar to the rapid IV infusion, although the absolute plasma concentrations were higher with IV infusion (Fig. 3). After intratracheal delivery of the lower dose of flecainide (0.75 mg/kg), both LV and venous plasma levels peaked (C_{max}) at 2 minutes (LV: $P < 0.05$; venous: $P < 0.05$, both compared with predrug baseline) and remained significantly elevated at 5, 10, and 15 minutes before progressively declining to lower levels at 30 minutes (LV: NS; venous: NS, compared with predrug baseline). After intratracheal instillation of the higher dose of flecainide (1.5 mg/kg), both LV and venous plasma levels also reached the C_{max} at 2 minutes (both, $P < 0.05$) and remained significantly elevated at 5, 10, and 15 minutes before declining to lower levels at 30 minutes (LV: NS; venous: $P < 0.05$ compared with predrug baseline).

Pharmacodynamics: Effects on Heart Rate and Mean Arterial Pressure

Neither rapid nor slower IV administration of flecainide (2 mg/kg bolus over 2 or 10 minutes) nor intratracheal instillation of 0.75- or 1.5 mg/kg doses of flecainide affected heart rate or mean arterial pressure across 30 minutes (Table 1). Similarly, intratracheal instillation of placebo had no effect on PD.

Pharmacodynamics: Effects on the QRS Complex and PR, JT_c, and QT_c Intervals

The QRS complex duration rapidly increased for 2 minutes and peaked at 5 minutes after intratracheal instillation of either 0.75- or 1.5-mg/kg doses of flecainide (Table 2). The lower dose caused a 10% increase in the QRS complex duration at 2 minutes ($P < 0.05$) and a 12% increase, the peak effect, at 5 minutes ($P < 0.05$). The higher intratracheal flecainide dose increased the QRS complex duration by 19% at 2 minutes ($P < 0.05$) and by 21%, the peak effect, at 5 minutes ($P < 0.05$). The QRS complex remained significantly prolonged at 10 and 15 minutes after administration of the higher intratracheal dose of the drug.

Rapid IV administration of flecainide (2 mg/kg bolus over 2 minutes) increased the QRS complex duration by 38% and 34%, coincident with increased plasma levels of the drug

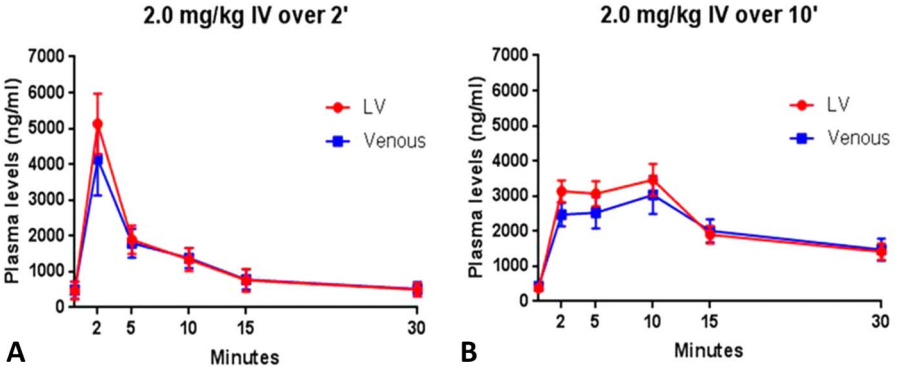

FIGURE 2. Flecainide plasma levels after intravenous (IV) infusion of 2.0 mg/kg over 2 minutes (Panel A) (N = 7) and 10 minutes (Panel B) (N = 8). $P < 0.05$ according to post hoc Dunnett's test comparing every time point to predrug baseline (0 minutes).

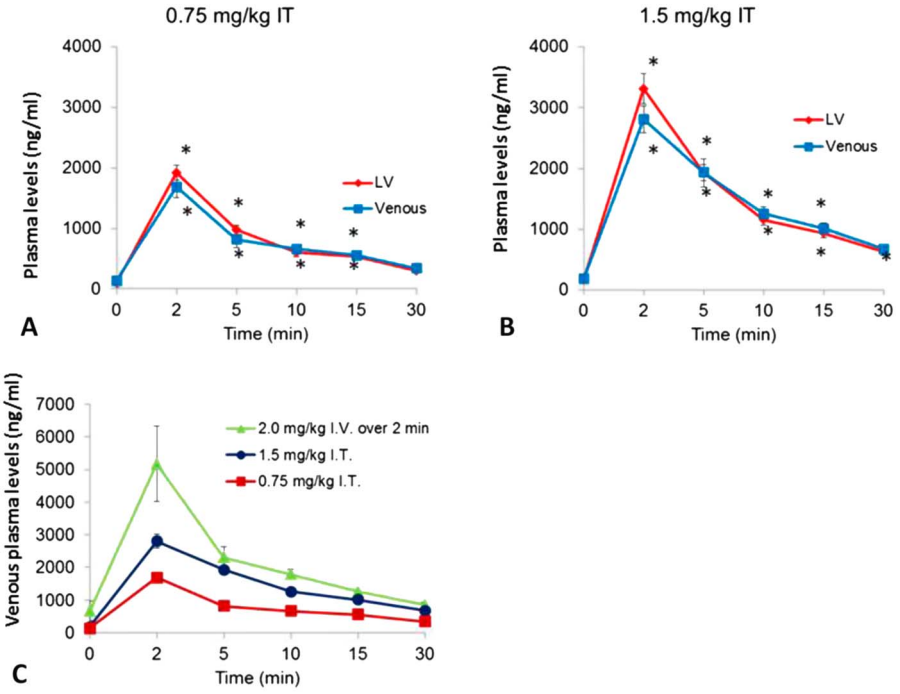

FIGURE 3. Flecainide plasma levels after intratracheal (IT) instillation of 0.75 mg/kg (Panel A, N = 5) and 1.5 mg/kg (Panel B, N = 5) and comparison to rapid IV infusion (Panel C, N = 7). *$P < 0.05$ according to post hoc Dunnett's test comparing every time point to predrug baseline (0 minutes).

at 2 and 5 minutes, respectively ($P < 0.05$) (Fig. 4). Thereafter, QRS complex duration progressively decreased to baseline levels at 30 minutes (NS). These PD responses were similar to those observed after intratracheal instillation. Slower IV infusion of flecainide (2 mg/kg bolus over 10 minutes) progressively prolonged the QRS complex as the plasma levels increased, achieving a maximum prolongation of 34% at 10 minutes ($P = 0.002$), and then declined but remained prolonged at 30 minutes.

Administration of the 0.75-mg/kg intratracheal dose of flecainide increased PR interval by 5% ($P = 0.02$) at 5 minutes; by 10 minutes, it had returned to baseline (ANOVA = 0.94) (Table 2). Intratracheal instillation of the 1.5-mg/kg dose increased PR interval by 13% ($P = 0.002$) at 5 minutes; by 10 minutes, it had returned to baseline (ANOVA = 0.09). Rapid IV administration of flecainide (2 mg/kg bolus over 2 minutes) caused an immediate 21% increase in PR interval at 2 minutes ($P < 0.05$), which remained prolonged at 30 minutes. IV infusion over 10 minutes increased PR interval by 21% at 10 minutes ($P = 0.004$), which also remained prolonged at 30 minutes.

Neither rapid nor slow IV nor intratracheal flecainide at 0.75- or 1.5-mg/kg doses affected the JT_c or QT_c intervals across 30 minutes (Table 2). There were no changes in any of these parameters in response to intratracheal instillation of saline solution.

TABLE 1. Absence of Hemodynamic Effects of Intravenous Infusion of Flecainide and Intratracheal Instillation of Flecainide and Placebo

	Pre-drug	2 min	5 min	10 min	15 min	30 min	*P*
Heart rate (beats/min)							
2.0 mg/kg IV over 2 min	100 ± 0.9	96 ± 2.6	96 ± 3.4	96 ± 2	92 ± 1.9	91 ± 1.3	0.3
2.0 mg/kg IV over 10 min	105 ± 7.3	109 ± 6.9	110 ± 6.4	107 ± 6.1	108 ± 6.1	108 ± 7.7	0.81
1.5 mg/kg IT	111 ± 7.2	116 ± 5.9	118 ± 6.7	115 ± 7	114 ± 6.7	115 ± 6.8	0.99
0.75 mg/kg IT	113 ± 7.1	115 ± 7.4	118 ± 7.4	114 ± 7.5	114 ± 7.4	114 ± 8	0.97
Placebo IT	111 ± 16.6	112 ± 13.6	110 ± 16.2	110 ± 15.6	111 ± 14.6	107 ± 15	0.98
Mean arterial blood pressure (mm Hg)							
2.0 mg/kg IV over 2 min	105 ± 10.4	90 ± 12.8	91 ± 12.5	94 ± 8.7	95.5 ± 21.5	94 ± 18	0.95
2.0 mg/kg IV over 10 min	99 ± 16.5	98 ± 17	95 ± 16	87 ± 15.8	91 ± 15.9	101 ± 17.9	0.54
1.5 mg/kg IT	108 ± 9.4	99 ± 10.1	99.8 ± 11.6	100.3 ± 11	102.8 ± 8.7	102 ± 9	0.99
0.75 mg/kg IT	110.5 ± 3.6	105.5 ± 4.9	108.8 ± 3.6	108.5 ± 3.8	110.5 ± 3.5	112 ± 5.3	0.91
Placebo IT	110.5 ± 0.5	111 ± 2	112.5 ± 0.5	107.5 ± 1.5	109 ± 2	112.5 ± 1.5	0.25

P-value = Significance according to ANOVA.
IT, intratracheal; IV, intravenous.

TABLE 2. Electrocardiographic Effects of Flecainide and Placebo

	Pre-drug	2 min	5 min	10 min	15 min	30 min	*P*
PR interval (ms)							
2.0 mg/kg IV over 2 min	106 ± 2.6	128 ± 5.9*	127 ± 5.1*	120 ± 4.9*	116 ± 6.1	114 ± 6.1*	<0.001*
2.0 mg/kg IV over 10 min	125 ± 3.6	127 ± 3.5	141 ± 3.9*	151 ± 5.4*	139 ± 5.7*	133 ± 5.3*	<0.001*
1.5 mg/kg IT	127 ± 2.3	141 ± 5.2	144 ± 4.6*	142 ± 4.7	136 ± 4.9	131 ± 4.8	0.09
0.75 mg/kg IT	130 ± 5.3	135 ± 5.1	137 ± 5.0*	136 ± 4.8	134 ± 5.4	132 ± 3.5	0.94
Placebo IT	124 ± 6.0	127 ± 6.0	128 ± 6.0	127 ± 8.0	128 ± 5.0	130 ± 6.0	0.99
QRS complex duration (ms)							
2.0 mg/kg IV over 2 min	61 ± 1.7	84 ± 6.5*	82 ± 2.8*	73 ± 1.1	70 ± 0.7	64 ± 2.4	0.002*
2.0 mg/kg IV over 10 min	56 ± 3.0	59 ± 2.6*	69 ± 3.2*	75 ± 3.5*	69 ± 3.5*	63 ± 3.3*	<0.001*
1.5 mg/kg IT	57 ± 0.4	68 ± 1.9*	69 ± 2.2*	67 ± 1.7*	64 ± 1.3*	60 ± 0.9	<0.001*
0.75 mg/kg IT	58 ± 1.8	64 ± 1.6*	65 ± 1.7*	64 ± 1.7	60 ± 0.9	58 ± 0.9	0.009*
Placebo IT	60 ± 3.0	58 ± 3.4	59 ± 2.9	58 ± 1.9	59 ± 2.8	59 ± 2.8	0.98
QT_c interval (ms)							
2.0 mg/kg IV over 2 min	450 ± 7.7	467 ± 4.8	466 ± 9.0	464 ± 8.2	469 ± 2.6	463 ± 0.1	0.58
2.0 mg/kg IV over 10 min	445 ± 12.9	440 ± 7.4	453 ± 7.1	460 ± 7.4	455 ± 6.3	447 ± 10.9	0.18
1.5 mg/kg IT	436 ± 7.1	464 ± 7.3	468 ± 8.9	463 ± 10.2	459 ± 9.9	450 ± 8.6	0.15
0.75 mg/kg IT	435 ± 13.0	454 ± 6.0	456 ± 6.4	453 ± 8.9	451 ± 7.3	447 ± 6.5	0.55
Placebo IT	430 ± 9.1	430 ± 8.4	428 ± 11.2	432 ± 10.1	432 ± 8.7	428 ± 13.3	0.97
JT_c interval (ms)							
2.0 mg/kg IV over 2 min	372 ± 9.5	361 ± 9.0	362 ± 8.7	372 ± 8.8	382 ± 2.5	384 ± 3.5	0.58
2.0 mg/kg IV over 10 min	364 ± 13.8	347 ± 10.4	348 ± 11.0	348 ± 12.2	352 ± 11.6	355 ± 14.6	0.47
1.5 mg/kg IT	362 ± 6.5	371 ± 6.2	371 ± 8.4	373 ± 8.6	376 ± 8.2	370 ± 8.0	0.36
0.75 mg/kg IT	349 ± 12.0	363 ± 5.8	364 ± 6.8	363 ± 9.0	363 ± 8.0	363 ± 7.8	0.81
Placebo IT	349 ± 7.3	353 ± 8.4	349 ± 11.5	355 ± 10.0	353 ± 9.2	351 ± 12.2	0.96

*Tabular data with $P < 0.05$ are significant according to post hoc Dunnett's test. Right column data with $P < 0.05$ are significant according to ANOVA.
IT, intratracheal; IV, intravenous.

Concentration–Response Relationship Between Venous Plasma Levels and QRS Complex Duration

Both the 0.75- and 1.5-mg/kg intratracheal doses yielded similar concentration-dependent increases in QRS complex duration compared with rapid 2.0 mg/kg IV infusion at their peak plasma levels at 2 minutes (Fig. 5). In comparison to rapid delivery, the IV infusion of flecainide over 10 minutes yielded a less steep, nonsignificant ($P > 0.90$) relationship between QRS complex prolongation and peak concentration of flecainide. Individual experiment data show a linear dose–response relationship between QRS complex increases and peak plasma levels of flecainide for the 2 intratracheal doses and the rapid IV infusion (r = 0.86). The magnitude of the effect on the QRS complex duration was correlated to plasma concentration of flecainide ($r^2 = 0.74$, $P < 0.001$) (Fig. 6).

DISCUSSION

This is the first study to determine the PK and PD effects on QRS complex and PR interval prolongation of

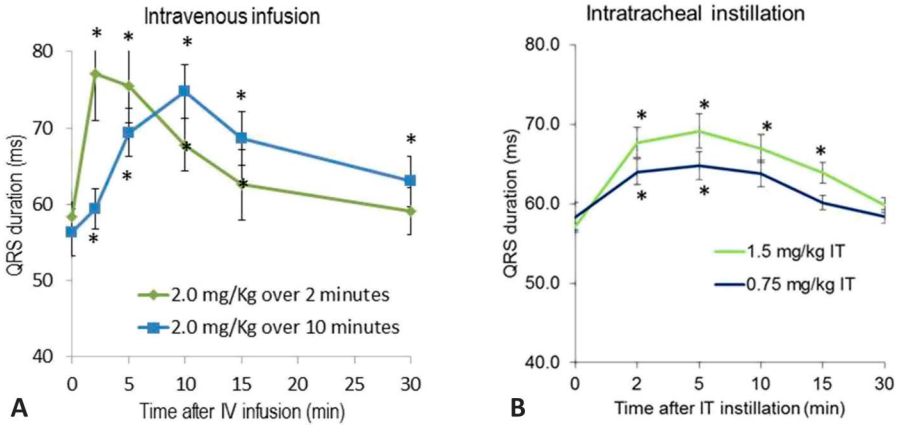

FIGURE 4. QRS complex duration at different time points after intravenous (IV) administration and intratracheal (IT) instillation of flecainide. Panel A: QRS complex duration after IV infusion of 2.0 mg/kg flecainide over 2 (N = 7) and 10 minutes (N = 8). Panel B: QRS complex duration after intratracheal (IT) instillation of 0.75 mg/kg and 1.5 mg/kg of flecainide (N = 5). *$P < 0.05$ according to post-hoc Dunnett's tests.

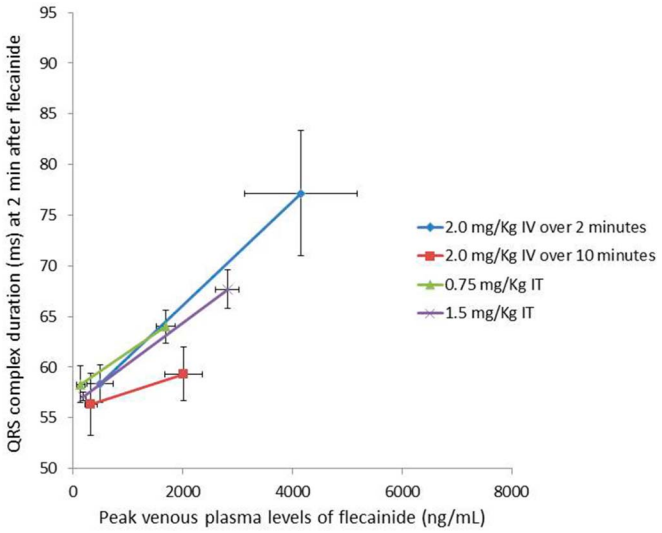

FIGURE 5. QRS complex duration as a function of peak plasma levels at 2 minutes after flecainide delivery via intratracheal (IT) instillation (N = 5) and with rapid, 2-minute (N = 7) and slow, 10-minute (N = 8) IV administration.

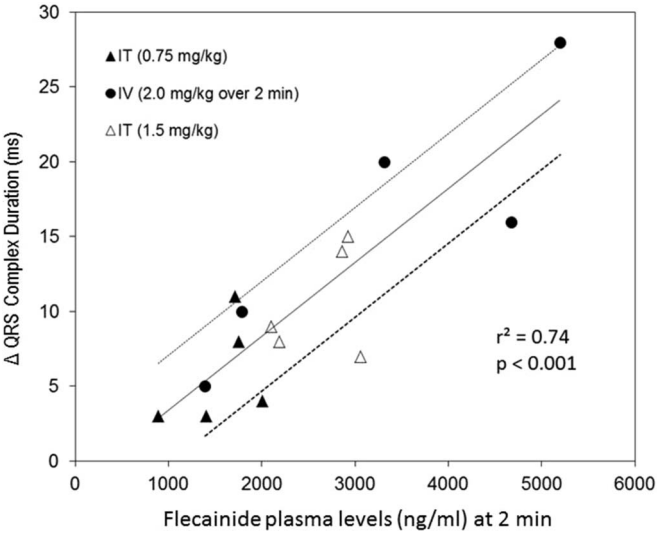

FIGURE 6. Dose–response relationship of the QRS complex increase and peak plasma levels of flecainide after flecainide delivery via intratracheal (IT) instillation of 0.75 mg/kg and 1.5 mg/kg and IV infusion of 2.0 mg/kg over 2 minutes (N = 5 for each group). Solid line represents linear regression trendline for predicted values. Dashed line represents the SE above and below the mean linear coefficient of regression.

flecainide delivered by intratracheal instillation compared with IV administration. The rationale for the present study derives from (1) successful clinical studies that tested the pill-in-the-pocket regimen with flecainide[4,6] to treat patients with occasional episodes of AF; (2) the fact that oral inhalation would potentially provide a more rapid and efficient delivery of the compound than oral administration; and (3) results of a recent clinical study in healthy volunteers showing that a handheld nebulizer delivers sufficient flecainide to elicit the expected ECG changes.[11,12]

Prior Studies

Flecainide has been widely used for treatment of both ventricular and supraventricular arrhythmias.[13] It has been shown to reduce the occurrence of premature ventricular complexes and to convert AF to sinus rhythm.[2,3,5,14] Chronic daily treatment with flecainide can cause adverse reactions including blurred vision, dizziness, depression of the left ventricular contractility, and proarrhythmia. To reduce complications associated with chronic, daily use of the drug, the PIP regimen has emerged as a possible solution, as exposure to the drug would be limited to periods of symptomatic arrhythmia. Alboni et al[4] reported that this strategy successfully treated 92% of all arrhythmic episodes in a trial of 165 patients with infrequent but recurrent episodes of AF in a follow-up period of 15 ± 5 months. Twelve of the subjects (7%) had adverse effects, including only 1 patient with an adverse cardiac response, specifically, atrial flutter with 1:1 atrioventricular nodal conduction. Recently, Andrade et al[9] reported that in clinical practice there is need for caution with respect to patient selection for the PIP regimen because of potential for adverse events such as flutter with 1:1 capture, conversion pauses leading to syncope, and hypotension that cannot always be predicted by the in-hospital oral administration of the drug.

Present Study

In the present preclinical study, we evaluated effects of intratracheal instillation and IV infusion of the class IC agent flecainide on standard electrocardiographic and hemodynamic parameters and plasma levels of the drug in anesthetized pigs.

Intratracheal instillation of flecainide generates a PK pattern similar to that of IV administration of flecainide, although the absolute plasma concentrations were higher with IV infusion. Specifically, a peak in plasma levels occurs at 2 minutes after delivery of the drug, consistent with rapid absorption of the solution through the lungs, airways, and alveoli. The distribution phase occurred between 2 and 5 minutes and was followed by the elimination phase throughout the remaining time. This profile is comparable to IV infusion of flecainide over 2 minutes, underscoring the efficiency of the lung delivery route using intratracheal instillation.

Intratracheal instillation of flecainide also generated a concentration–response relationship between QRS complex and peak plasma levels that was similar to that of rapid IV infusion. Although none of the flecainide doses and delivery routes caused significant changes in the JT_c or QT_c intervals or in heart rate or MAP, we found significant increases in the QRS complex duration after intratracheal instillation ranging from 10% to 19% at 2 minutes and from 12% to 21% at 5 minutes with the 0.75 and 1.5 mg/kg doses, respectively. This finding is consistent with a clinical report by Hellestrand et al[15] of a greater effect of flecainide on His-Purkinje and ventricular conduction than on atrioventricular nodal conduction.

In future studies, it will be important to explore the use of aerosol methods for lung delivery of drug instead of intratracheal instillation.

CONCLUSIONS

This study carries significant implications by successfully describing a potential novel means for treating cardiac arrhythmias. Our results reflect the fact that an increase in the QRS complex is the primary antiarrhythmic effect of flecainide and suggest that intratracheal instillation of the agent would be warranted in further experimental investigation of the effects of pulmonary delivery of flecainide on experimental models of supraventricular and ventricular arrhythmias. Importantly, the results of the present study are consistent with the results of a recent phase 1 study in healthy volunteers, showing that flecainide delivered via oral inhalation using a handheld nebulizer yielded plasma levels sufficient to prolong the QRS complex and PR interval.[11,12]

Thus, intratracheal delivery of flecainide generates a PK and PD relationship comparable to that of IV administration. Both modes of delivery elicited ECG changes that were consistent with the pharmacological activity and efficacy of flecainide.

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