A Novel Approach to Deliver Flecainide to the Heart: A Study in Healthy Volunteers
to Compare the Cardiovascular Effects of Inhaled vs Intravenous Flecainide

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Introduction

Flecainide (FLEC) is effective for cardioversion of recent-onset atrial fibrillation (AF). In dogs and pigs intratracheal instillation of FLEC is effective in terminating episodes of AF within minutes. This study is part of a drug development program to use inhaled (IH) of FLEC to cardiovert paroxysmal AF. In this open-labeled 2-period crossover study, we compared the effects of FLEC administered via IV and oral IH on QRS, and PR interval duration, heart rate (HR), blood pressure (BP), and FLEC plasma levels.

Methods

Six healthy volunteers were randomized to receive FLEC via either IV infusion over 10 min (~150 mg) or IH delivered with a median time of 4.5 mins (estimated total lung dose = 30 mg).

• Subjects were monitored for pulmonary and cardiac function.

• Time points for analyzing ECG recordings and for blood sampling for pharmacokinetic analysis were identical in periods 1 and 2.

• IH delivery was performed using a Trudell AeroEclipse II BAN jet nebulizer. Values are means ± SEM.

Phase 1 Clinical Study

Open Labeled, Two Period Randomized (IV) vs. Inhalation (IH) Cross-over Study

<table>
<thead>
<tr>
<th>Route</th>
<th>Group A</th>
<th>Group B</th>
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<tbody>
<tr>
<td></td>
<td>2 mg/kg</td>
<td>30 mg</td>
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<tr>
<td>Infusion</td>
<td>7-10 am</td>
<td>Group B</td>
</tr>
<tr>
<td>Inhalation</td>
<td>30 mg &amp; 2 mg/kg</td>
<td>Group A</td>
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Position of the subjects during the study


Results

• There were no differences in baseline values of HR, BP, or QRS or PR intervals for periods #1 and #2 (Figure 1).

• Peak FLEC plasma concentrations were 749±308 ng/mL for IV and 120±70 ng/mL for IH (Figure 2).

• Time to Cmax (Tmax) for post dosing were 1 and 0.5 min for IV and IH, respectively. Distribution and elimination half-lives were nearly identical (Table 1).

• PK parameters for IV and IH FLEC had similar concentration-time profiles (Figure 3 and Table 1).

• The maximal increases (Δ) in QRS interval duration were 36±3 msec (FLEC-IV) vs. 15±7 msec (FLEC-IH) (Figure 4).

• QRS interval remained prolonged for up to 60 min post FLEC-IV; following FLEC-IH, QRS duration returned toward pre-dose values within 15-30 min (Figure 4).

• Following FLEC-IV, systolic BP decreased ~15 mmHg and HR increased by ~8 bpm. FLEC-IH was associated with a 5-6 bpm HR increase and variable changes in BP (+4 to -5 mmHg) (Figure 5).

• No serious adverse events (AEs) were reported (Table 2).

• There were minimal or no changes in pulmonary spirometry.

Conclusions

• Low-dose FLEC-IH is safe and well-tolerated and delivers FLEC into the systemic circulation with T1/2 of ~1 min in sufficient amounts to prolong the QRS interval.

• The large surface area of the lung (~100m²), highly vascularized and permeable alveolar-vascular region explain the rapid delivery of FLEC to the heart.

Disclosures

LB, NR, and PM are employed by InCarda Therapeutics. Beth Israel Deaconess Medical Center employs RLV, ACS, and VZZ and received a grant from InCarda for analyses of these data. DS and SS conducted the study under a grant from InCarda Therapeutics.