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. The present 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

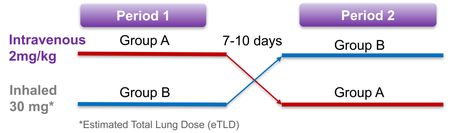
Six healthy volunteers were randomized to receive FLEC via either IV infusion over 10 min (2 mg/kg, ~150 mg) or IH delivered with a median time of 4.5 mins (estimated total lung dose = 30 mg)

- 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 Intravenous (IV) vs. Inhalation (IH) Cross-over Study

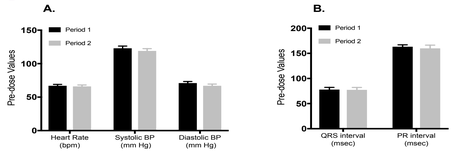


Position of the subjects during the study
- Oral IH: Semi-recumbent -- seated upright - semi-recumbent
- IV Infusion: ----------semi-recumbent ----------

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 C_{max} (T_{max}) 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-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.

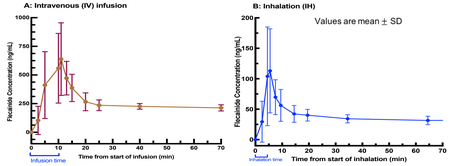
Figure 1 - Period 1 and Period 2: Pre-Dose Values of Vital Signs and ECG Intervals



Values are mean ± SEM @ 15 min prior to dosing

Figure 2 - PK Curves of Flecainide Administered via IV and Inhalation

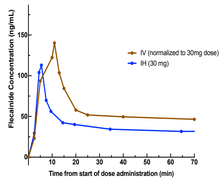
Venous plasma concentration of flecainide following intravenous (IV) infusion and oral inhalation (IH) of flecainide



Panel A: 2 mg/kg, over 10 min (~150 mg); n=6

Panel B: 30 mg, median inhalation time = 4.5 min; n=6

Figure 3 – Shorter T_{max} for Inhalation vs. IV infusion



- **Comparable overall systemic disposition of flecainide following administration by these two routes.**
- **The estimated pulmonary bioavailability of flecainide given via IH is ~ 75%.**

Table 1 - Pharmacokinetics of Flecainide Administered via IV Infusion and Inhalation

Dose and Route of administration	t_{max} min	C_{max} ng/mL	AUC_{Ls} st Hr*ng/mL	Dist. $t_{1/2}$ min	Elim. $t_{1/2}$ hours
Inhaled (30 mg) n=6	0.5 (0, 1)	120 (59)	487 (20)	4.28# (36)	10.1 (20)
IV (2 mg/kg, 150 mg) n=6	1 (0, 60)	749 (41)	3051 (11)	4.67# (30)	10.0 (18)
IV (2 mg/kg) n=3*	10.0	1644±534	4211±456	2.6±0.7	9.3±1.0

All values for inhaled flecainide are arithmetic mean (CV%) except t_{max} values (measured from end of inhalation) which are median (min, max).

Values for IV flecainide from the literature (Row #3 in table above) are Mean ± SEM.

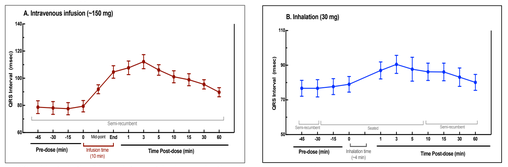
#Data from 1 subject in the IH arm and 2 subjects in the IV arm could not be estimated.

Data source: Table 14.2.2.3-B

*http://www.eisai.jp/medical/products/dj/EPI/TMB_A_EPI.pdf

The distribution and elimination phases are independent of the route of administration and dose

Figure 4 - Time Course of Changes in QRS Interval Duration Following Administration of Flecainide via IV and IH



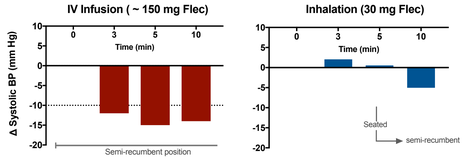
In 3/6 subjects in the IV arm, intraventricular conduction delay lasted approximately 15 min

Values are mean ±SEM

*10 min IV infusion of a total dose of 149±17 mg.

** 4 min inhalation

Figure 5 - Administration of Flecainide via IV (but not IH) Lowers the Svstolic BP Post-dose



Note: In one subject of the IV arm, the IV infusion of flecainide was stopped because systolic blood pressure dropped below 70 mmHg and, in 4/6 subjects a decrease in BP ≥ 10 mm Hg was recorded.

Table 2 - Common Treatment-Emergent Adverse Events

Inhalation

Adverse Events	n
Oropharyngeal discomfort	4
Chest discomfort	1
Oral paraesthesia	1
Shortness of breath	1
Cough / Hoarseness of throat	1

Source: Table 14.3.1.2-B

Intravenous

Adverse Events	n
Lightheadedness / dizziness	6
Headache	5
Oral paraesthesia	3
Discomfort at site of injection	2
Dry Mouth/Throat	2
Ocular discomfort	1
Fatigue	1

Source: Table 14.3.1.2-B

Total number of TEAEs reported were:
49 following IV infusion: 35 probably related; 1 SEVERE, 3 MODERATE, 31 MILD
12 following inhalation: 9 probably related; ALL MILD

Conclusions

- Low-dose FLEC-IH is safe and well-tolerated and delivers FLEC into the systemic circulation with at T_{max} 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 VZD and received a grant from InCarda for analyses of these data. DS and SS conducted the study under a grant from InCarda Therapeutics.