Hand-held Breath-Actuated Nebulizer for Delivery of Flecainide to the Heart: Dose-Concentration Dependent Pharmacokinetics and QRS Interval Prolongation of Inhaled Flecainide in Healthy Volunteers

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Introduction

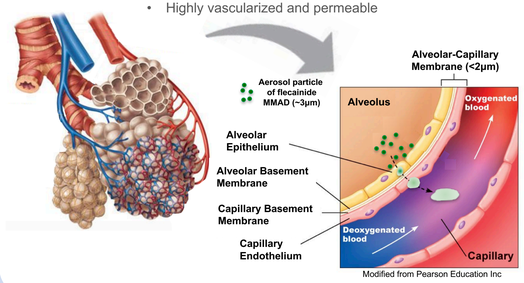
Oral and IV routes for delivery of flecainide (FLEC) for acute cardioversion of atrial fibrillation (AF) have drawbacks: high doses (150-300 mg) and 2- to 4- hours wait time for cardioversion with oral dosing and hospitalization for IV administration. Studies in large animal models of AF suggest that FLEC administered via inhalation (IH) may convert AF rapidly at relatively low doses. Thus, FLEC-IH could be effective at low doses and shorten the time to cardioversion to minutes without requiring emergency room visits.

Hypothesis

We hypothesized that because of the large surface area of the lung (~100m²), rapid delivery of FLEC to the heart can be accomplished via oral inhalation.

Schematic of Alveolar-Vascular Region

- Large surface area (~100m²)
- Highly vascularized and permeable



Modified from Pearson Education Inc

We investigated whether FLEC-IH could rapidly deliver sufficient drug to elicit its "signature" electrophysiological effect, QRS interval prolongation.

Methods

A double-blind, randomized, placebo-controlled study consisting of sequential single ascending estimated lung doses of FLEC solution or matching placebo (PL) administered with a hand-held inhaler (Trudell AeroEclipse II BAN) was undertaken (FLE-001).

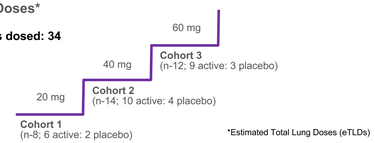
Subjects (n=34) were randomized and assigned to cohorts (FLEC/PL): #1 (20 mg; 6/2), #2 (40 mg;10/4) and #3 (60 mg; 9/3). Doses administered are estimated total lung doses.

Monitoring included pulmonary and cardiac function using lung spirometry, continuous ECG, blood pressure (BP), and heart rate (HR).

Phase 1 Clinical Study

Double-blind, Randomized, Placebo controlled, Three Single Ascending Doses*

Total subjects dosed: 34
Active: 25
Placebo: 9

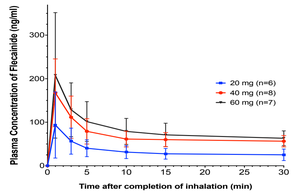


*Estimated Total Lung Doses (eTLDs)

Results

- FLEC-IH caused dose-concentration dependent increases in plasma levels (Figure 1 and Table 1) and QRS interval duration (Figures 2 and 3).
- Half-lives for distribution (3-4 min) and elimination (9-12 hrs) of FLEC-IH were dose-independent (Table 1), similar to those reported for FLEC-IV (4.7±1.4 min and 10.0±1.8 hrs).
- Figure 3 shows the time course of changes in QRS interval duration following FLEC-IH and PL.
- No serious adverse events (AEs) were reported. All AEs except one (moderate) were mild; most common was oropharyngeal discomfort (Table 2).

Figure 1 - Inhaled Flecainide at 20, 40 and 60 mg Exhibits Near-Dose Proportionality (FLE-001)



Mean venous plasma concentration-time curves following oral inhalation of flecainide acetate solution

Values are mean ±SD
Doses are estimated total lung doses (eTLDs)

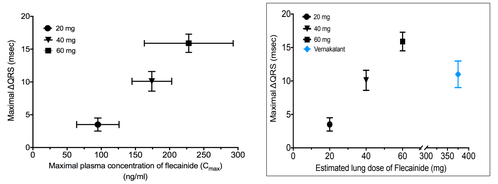
Table 1 - Pharmacokinetic Parameters of Flecainide Administered via Inhalation

Route of administration	t_{max} min	C_{max} ng/mL	AUC_{Last} Hr.ng/mL	Elim. $t_{1/2\beta}$ hours	Dist. $t_{1/2\alpha}$# min
Inhaled (20 mg) n=6	1 (1, 3)	95.1 (79)	421 (45)	9.87 (25)	3.86 (34)
Inhaled (40 mg) n=8*	1 (0, 1)	173 (47)	685 (26)	9.0 (24)	4.19 (39)
Inhaled (60 mg) n=7*	1 (0, 3)	232 (78)	946 (22)	12.0 (14)	3.47 (17)

All values for inhaled flecainide are arithmetic mean (CV%) except t_{max} values (measured from end of inhalation) which are median (min, max).
*Based on PK cut-off criteria of t_{max} ≥ 15 min, data from 2 subjects of each cohort were excluded.
#Data from 1 subject of the 20 and 40 mg cohorts and 4 subjects of the 60 mg cohort could not be estimated.
Data source: Table 14.2.2.6-A (Cohorts 1, 2 and 3).

Distribution and elimination half-lives are independent of the dose of flecainide

Figure 2 - Dose–Concentration Dependent Increases in QRS Interval Duration Following Inhalation of Flecainide in Healthy Volunteers

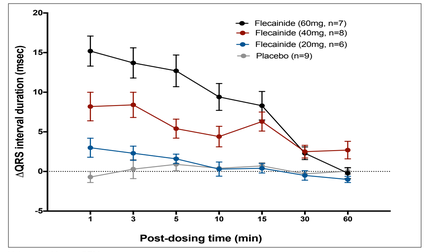


Values are mean ± SEM.

◆The data for vernakalant are from the results of a Phase 1 study in healthy volunteers. Vernakalant was given at a dose of 5 mg/kg via IV infusion over 10 mins (Cardiovascular and Renal Drugs Advisory Committee of the FDA, 11 December 2007.)

Figure 3 - Time Course of Changes in QRS Interval Duration (ΔQRS) Following Oral Inhalation of Flecainide

Double-blinded, randomized active vs. placebo study



Values are Mean ± SEM.
Values for the ΔQRS are relative to the pre-dose. QRS interval durations were obtained from Lead V4 of 12-lead ECGs of 30 healthy volunteers. Data for the placebo group are from all three cohorts of Part A study.

Table 2 - Common Treatment-Emergent Adverse Events* (Combined pooled data for cohorts 1, 2, 3 and placebo)

Adverse Events	Placebo (n=9)	Flecainide (n=25)
Oropharyngeal Discomfort	2 (22%)	10 (40%)
Shortness of breath	-	4 (16%)
Cough	-	3 (12%)
Dry Mouth	1 (11%)	3 (12%)
Lightheadedness	1(11%)	3(12%)

Source: Table 14.3.1.2-A

*Probably and possibly study-drug related
No Severe adverse events were reported
Only 1 subject reported moderate adverse events: dizziness and oropharyngeal discomfort
No dose-dependent reporting of the following AEs: cough, difficulty breathing
For oropharyngeal discomfort and dry mouth, more subjects from Cohorts #2, #3 reported these AEs than those from Cohort #1 (No difference in frequency between cohorts #2 and #3)

Conclusions

FLEC-IH prolongs QRS interval in a dose-concentration dependent manner, consistent with its established pharmacological and therapeutic effects.

Disclosures

LB, NR, CS 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.