**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 2-4 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 (~100m²), rapid delivery of FLEC to the heart can be accomplished via oral inhalation.

**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 (FLEC-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).

**Results**

- **FLEC-IH caused dose-concentration dependent increases in plasma levels (Figures 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).

**Conclusions**

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

**Disclosures**

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