Abstract: P3810

Hysteresis between pharmacokinetics and changes in QRS complex duration following flecainide administered via oral inhalation or IV infusion

Authors:
P. Madhavapeddi¹, R.L. Verrier², L. Belardinelli¹, ¹InCarda Therapeutics, Inc. - Newark, California - United States of America, ²Harvard Medical School - Boston - United States of America,

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Background: The class IC antiarrhythmic agent flecainide is being developed for delivery via oral inhalation for the management of acute episodes of recent onset atrial fibrillation. Widening of the QRS complex is a known pharmacodynamic effect of flecainide.

Purpose: Data from a recently completed Phase 1 study were analyzed to determine whether the relationship between the pharmacokinetics (PK) and the pharmacodynamics (PD), measured by changes in QRS, of flecainide delivered by oral inhalation are similar to those when delivered via IV infusion.

Methods: This Phase 1 study in 6 healthy volunteers was carried out to assess the PK and PD of flecainide delivered via IV infusion over 10 minutes (2 mg/kg, ~ 150 mg) vs. oral inhalation delivered over 4.5 minutes (estimated total lung dose, eTLD of 30 mg) using a 2-period crossover design study. Oral inhalation was performed using a hand-held inhaler (Trudell AeroEclipse II BAN). Venous plasma samples were drawn and ECGs were recorded at various times pre-, during and post-dosing.

Results: A non-steady-state relationship between the PK and PD of flecainide was observed when delivered via either IV or inhalation. As shown in the figure, there was a lag (i.e., delay) between the prolongation of the QRS (ΔQRS) and the changes (rise and decline) in plasma levels of flecainide, following its administration by either route. The lag time between Tmax (time to peak plasma of flecainide) and time to maximal QRS interval prolongation was 2.7±3.9 min and 3.4±2.1 min (mean SD, n=6) following IV infusion and oral inhalation of flecainide, respectively. Not shown, as the rise and decline of plasma concentrations of flecainide precede the changes in QRS complex duration, the time-matched relationship between them is described by counterclockwise hysteresis loops.

Conclusion: The PK-PD relationship of flecainide following either IV or inhalation was essentially identical except for the difference in duration of dosing (4.5 min for inhalation; 10 min for IV infusion), higher plasma levels of flecainide, and greater ΔQRS complex duration following IV administration of flecainide as a result of the higher dose. The temporal displacement between the ΔQRS complex duration and the changes in venous concentrations of flecainide are characteristic of a distributional non-equilibrium across the heart, leading to hysteresis.
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Authors: P. Madhavapeddi 1, R.L. Verrier 2, L. Belardinelli 1
1 InCarda Therapeutics, Inc.­ Newark, California­ United States of America, 2 Harvard Medical School­ Boston­ United States of America

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PK-PD of IV vs. inhaled flecainide