Effect of a Lipid Nanoparticle Prodrug Formulation of Treprostinil (INS1009) on the Cough Reflex in Guinea Pigs

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Inhaled treprostinil (TRE) is a pulmonary vasodilator developed for the treatment of pulmonary arterial hypertension (PAH). Inhaled treprostinil prodrug–lipid nanoparticle (TPD-LNP; ~100 nm in diameter). Schematic representation of (A) treprostinil prodrug (TPD) - hexadecyl treprostinil (C16TR), (B) treprostinil (TRE), and (C) TPD-LNP: Schematic Comparison

RESULTS

Figure 3. Plethysmograms of 1 guinea pig showing 1 cough “bout” evoked by 10 min exposure to TRE (30 µg/mL). Each arrow at the bottom of the respiratory flow signal indicates a cough effort. For some of the coughs, virtually no cough sounds were detected. With a 10-min exposure to TRE, coughs were associated with between 1 and 4 cough bouts (number of coughs per bout varied).

Figure 4. Plethysmograms showing the absence of cough response in the same guinea pig with the second and third TRE exposures despite higher TRE concentrations. The interval between consecutive exposures was 2 hours.

Figure 5. Dose-dependent cough response in guinea pigs. Values are mean ± standard deviation of the mean. Values in parentheses represent the number of guinea pigs experiencing coughed mucus.

CONCLUSIONS

• The main finding of this study is the absence of cough in guinea pigs after administration of inhaled C16TR-LNP (INS1009), whereas inhaled TRE induced a robust cough response.

• Two hypotheses are proposed to explain the absence of cough with inhaled C16TR-LNP (INS1009):
  – Concentrations of TRE at the pulmonary sensory nerves are below the threshold for activation.
  – The LNP formulation bypasses airway sensory nerves important for causing cough.

• Cough counts increased by 2-3 fold with inhaled phosphate-buffered saline (PBS) and inhaled C16TR-LNP, whereas inhaled TPD-LNP had no effect.

REFERENCES


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