Inhaled INS1009 Demonstrates Localized Pulmonary Vasodilation
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INTRODUCTION

INS1009 (treprostinil in a lipid nanoparticle) is a long-acting pulmonary vasodilator intended for inhalation. It is delivered through a nebulizer as a single-dose powder. The study described herein evaluated the effect of INS1009, delivered via a pneumatically driven nebulizer, on pulmonary arterial pressure (PAP) in the anesthetized rat.

AIMS

• To assess whether a single inhaled dose of INS1009 in rats pulmonary vasodilator activity up to 24 hours.

• To investigate if local delivery can reduce lung contributions to the prolonged pulmonary vasodilation with inhaled INS1009.

METHODS

Aerosol Delivery

Male Wistar Han rats were exposed to INS1009 at pulmonary doses of 0.57, 2.84, and 28.4 µg/kg (0.36, 1.8, and 18 µg/kg subcutaneously). The INS1009 aerosol was generated through a pneumatically driven nebulizer. The aerosol droplet distributions were characterized using an optical particle sizer. The nasal uptake efficiency was determined using a nose-only exposure system. The chemical formula of C39H66O5 was determined through a mass spectrometry analysis. The rats were exposed to INS1009 at 30 minutes before and during the assessment of pulmonary vascular hemodynamics in response to U46619 challenge.

RESULTS

• Aerosol delivery of INS1009

  - The average MMAD of the aerosol delivered to the nose port was 2.36 ± 0.16 µm. Data are captured in Table 1.

  - The aerosol delivery efficiency was determined through a nose-only exposure system and was 20%.

  - The chemical formula of C39H66O5 was determined through a mass spectrometry analysis.

• Intravascular Injection

  - U46619-induced increase in PAP was inhibited by intravenous infusion of INS1009.

• Vascular Hemodynamics

  - In anesthetized rats, pulmonary vasodilation was more prolonged with INS1009 compared with TRE with activity up to 3 hours, the maximum duration for this model.

• Inhaled INS1009

  - At the highest dose (28.4 µg/kg), INS1009 inhibited the U46619-induced increase in PAP up to 24 hours.

• Aerosol Delivery by the subcutaneous, intravenous, oral, and inhaled routes of administration. It is not certain to what extent the contribution of the lung vasculature to the systemic arterial blood pressure, and heart rate were measured in anesthetized, ventilated rats before (baseline) and after intra-arterial injection of the thromboxane mimetic U46619. Each rat was exposed to INS1009 at pulmonary doses of 0.57, 2.84, and 28.4 µg/kg over 24 hours.

CONCLUSIONS

• Inhaled INS1009 protects from U46619-induced pulmonary vasoconstriction up to 24 hours after a single inhaled dose.

• The effectiveness of TRE at preventing pulmonary vasoconstriction suggests that inhaled INS1009 has significant local activity and does not contribute significantly to systemic effects.

REFERENCES


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DISCLOSURES

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