Nebulization Patterns Affect Airway Hyperresponsiveness in Mice

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Abstract

The motivation of this study was to examine how factors other than drug concentration affect the bronchoconstrictor response to inhalation bronchoconstrictor agents such as methacholine (MCh). MCh-induced bronchoconstriction in mice has been shown to be dose-dependent and to be affected by factors such as nebulization pattern, nebulizer type, duty cycle, and particle size. However, the specific effects of these factors on the bronchoconstrictor response remain unclear. The aim of this study was to evaluate the effect of factors other than drug concentration on the bronchoconstrictor response to inhaled aerosolized MCh.

Background

The physiological response to an inhaled bronchoconstrictor challenge can potentially be influenced by various factors such as:

- The drug concentration
- The type of nebulizer
- The duration and rate of nebulization
- The disease state and severity

Objectives

Evaluate the effect of factors other than drug concentration on the physiological response to an aerosolized bronchoconstrictor challenge in mice.

Methods

Protocol

- Male A/J mice
- Anaesthetised, tracheostomised
- Connected to flexiVent for mechanical ventilation
- 150 breath/min, 10 mL/kg, FFPE = 5 cm H2O
- Aerosolised methacholine (MCh)
- Nebulizers: standard and fine mist
- Nebulizer type:
  - Standard (4-6 µm)
  - Fine Mist (2.5-4 µm)

Experimental Conditions

- Nebulizing time: 2.5-20 s
- Nebulizer rate (duty cycle): 25-100%
- Nebulizer type:
  - Standard (4-6 µm)
  - Fine Mist (2.5-4 µm)
- Humidity:
  - Presence of drying tube on air intake
  - Absence of drying tube on air intake

Lung Function Measurements

- SnapShot-150, Quick Prime II
- At baseline
- After MCh challenge (0-200 mg/mL)
- 12 measurements
  - Every 10 s
  - Alternating perturbations
- Between MCh challenges

Parameters: R, E, Rs, G, H

Results

Nebulization Patterns

- Standard nebulizer: 10s
- Fine mist nebulizer: 2.5s

Nebulizer Rate (Duty Cycle)

- Nebulization time: 2.5-20 s
- Nebulizer type:
  - Standard: 50%
  - Fine mist: 50%

Humidity Control

- 100 vs 75% relative humidity
- Nebulizer duty cycle

Nebulizer Characterization

- Nebulizer particle size
- Nebulization time
- Nebulizer rate

Summary

- FoT parameters augmented with increasing MCh.
- MCh-induced bronchoconstriction was independent of:
  - Nebulizer time
  - Nebulizer particle size
  - Humidity control (45% relative humidity)
- Inversely related to nebulizer duty cycle

Conclusions

- All aspects of the nebulization process must be considered when designing inhaler bronchoconstrictor protocols.
- The nebulizer duty cycle influenced the sensitivity of the physiological response to MCh.
- Effect presumably associated with particle agglomeration.
- Optimised physiological lung responses to an aerosol challenge can be obtained by adequate control over the nebulizer settings.

Disclosure

The authors declare no competing interests.

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