Safety Pharmacology Society Webinar:

Respiratory Safety Pharmacology

Strategy and Methodologies

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Overview

- Structural & Functional Components of the Lung
  - What functions need to be measured?
  - What measurement endpoints are typically used?

- Methodologies
  - Procedures & Equipment
    - Ventilatory Function
    - Lung Function (Mechanics)

- Drug-Induced Effects
  - Examples demonstrating measurement endpoints
Evaluation of Respiratory Functions

Pumping Apparatus
- **Function**: Regulate gas exchange between environment and airways
  - **Components**: Respiratory muscles, CNS, chemo/mechano-receptors
    - **Core Measurements**: Tidal volume, respiratory rate, minute volume
      - **Investigative Measurements**: Inspiratory and expiratory times, inspiratory and expiratory flows, end-inspiratory and end-expiratory pauses, apneic time, arterial blood gases (PaO₂/PaCO₂)

Gas Exchange Unit
- **Function**: Regulate gas exchange between airways and blood
  - **Components**: Airways, alveoli, vasculature, fibrous network
    - **Core Measurements**: Dynamic airway resistance and lung compliance
      - **Investigative Measurements**: Flow-Volume maneuver (PEF, FEV, FEF75, FEF25), Pressure-Volume maneuvers (Cst, IC, FVC, FRC), Gas Diffusion Capacity (DLCO)
Many procedures are available for assessing respiratory function – want to focus on procedures considered most appropriate for Safety Pharmacology:

- Are well established and physiologically based
- Are appropriate for Safety Studies
  - Utilize conscious, non-restrained animals (when possible)
  - Provide a direct measure of endpoints (when possible)
    - Minimizes the incidence of false negative and false positive results
  - Provide translational endpoints
Procedures for Ventilatory Function

• Ventilatory Patterns
  • Respiratory Rate & Tidal Volume
    • Plethysmograph Chambers
      • Head-out or Head-enclosed volume displacement chambers
        • Chamber pressure changes = lung airflow = tidal volume & breathing rate
    • Facemask with Pneumotachometer
      • Differential pressure change = Mouth airflow = tidal volume & breathing rate
    • Inductance Straps or Impedance electrodes
      • Thoracic and abdominal movement = lung airflow = tidal volume & breathing rate
Functional Endpoints

$V_E$ - Minute Volume ($V_T \times f$)

$f$ - Breathing Rate

$V_T$ - Tidal Volume

PIF - Peak Inspiratory Flow

PEF - Peak Expiratory Flow

FIT - Fractional Inspiratory Time $\frac{(T_i)}{(T_{tot})}$

AT - Apneic Time
Mouse Methyl Isocyanate Inhaled Irritant

End-inspiratory pause (activation of upper airway sensory neurons)

End-expiratory pause (activation of pulmonary irritant (C-fiber) receptors)

Ferguson, et al., Tox. Appl. Pharmacol. 82, 1986
Procedures for Lung Function

• Airway Resistance & Lung Compliance
  • Dynamic Measurements
    • Spontaneously breathing
    • Ventilated
  • Dynamic Restrained Models
    • Head-out or head-enclosed plethysmograph chambers, facemask with pneumotachometer
      • Lung airflow & volume
    • pressure sensitive catheter
      • Pleural pressure
        • esophageal, pleural or subpleural space
  • Dynamic non-restrained Models
    • Inductance straps or impedance sensors + pleural pressure
  • Static Anesthetized/Paralyzed Model
    • Forced maneuvers (plethysmograph +/- pleural pressure)
Measuring Dynamic Resistance and Compliance

Relationship of pulmonary flow and volume to transpulmonary pressure

$$\Delta P = (\Delta F \times R) + (\Delta V/C)$$

if $\Delta V = 0$ (isovolume points on insp and exp)

$$\Delta P = \Delta F \times R$$

$$R = \Delta P/\Delta F$$

if $\Delta F = 0$ (beginning and end of inspiration)

$$\Delta P = \Delta V/C$$

$$C = \Delta V/\Delta P$$
Functional Endpoints

Dynamic Compliance \[= \frac{\Delta V}{\Delta P} \] (At zero flow points)

Dynamic Resistance \[= \frac{\Delta P}{\Delta F} \] (At isovolume points)

Dynamic Conductance \[= \frac{\Delta F}{\Delta P} \] (At isovolume points)
Models – Conscious Restrained
Intervening Respiratory Monitoring in a Restrained Rat

- Tidal Volume (mL)
- Respiratory Rate (breaths/min)
- Minute Volume (mL/min)
- Total Pulmonary Resistance (mmHg/(mL/sec))
Conscious Non-Restrained

Whole Body Plethysmograph

Thoracic Impedance Change
(impedance electrodes & telemetry)

Thoracic/Abdominal Movement
(inductive straps & telemetry)
Continuous Respiratory Monitoring in a Non-restrained Primate

Dark Photoperiod
7-19 hrs post dose
Models – Indirect Measures of Airway Resistance

Penh – change in expiratory flow

Phase shift or Phase Angle ($\theta$)
(thoracic vs nasal flow)

Phase shift or Phase Angle ($\theta$)
(thoracic vs abdominal movement)

Whole Body

Dual Chamber (Conscious)
A – Phase angle (θ) = 180°; Phase Relation = 0% (paradoxical)
B – Phase angle (θ) = 90°; Phase Relation = 50% (asynchrony)
C – Phase angle (θ) = 0°; Phase Relation = 100% (synchrony)
Anesthetized Model in a Rat

Forced Manuevers Procedure

Flow-Volume Maneuver

Functional Endpoints

- PEF - Peak Expiratory Flow
- FEV₁₀₀ₐ₀ - Forced Expiratory Volume at 0.1 second
- FEF₇₅ - Forced Expiratory Flow at 75% of FVC
- FEF₂₅ - Forced Expiratory Flow at 25% of FVC
- IC - Inspiratory Capacity
- FVC - Forced Vital Capacity

Pressure - Volume Maneuver

Functional Endpoints

- IC - Inspiratory Capacity
- FVC - Forced Vital Capacity
- QLC - Quasistatic Lung Compliancem