Non-invasive airway resistance measurements in large animals by high frequency airwave oscillometry

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Abstract

Large animals are generally more sensitive than rodents to drug induced respiratory changes. Methodologies to measure airway resistance in large animals normally require an esophageal pressure probe placed under anesthesia or a surgically implanted pleural pressure catheter. Both approaches could alter experimental endpoints in toxicology studies, which limit their use in drug development. A non-invasive methodology to measure airway resistance by high frequency airwave oscillometry was evaluated in conscious Beagle dogs and cynomolgus monkeys. A forced oscillation system was used to assess airway resistance and obtain conventional respiratory parameters (tidal volume, respiratory rate) before and after an intravenous treatment with a bronchoactive agent. Respiratory mechanics measurements were performed using 16 second long single (19 Hz) frequency waveform, which was applied at each time point at the subject’s airway opening via a face mask. During measurements, pressure and flow signals were recorded. Between measurements, the animal was disconnected from the device and face mask, which facilitated data capture in conscious animals. After collection of baseline measurements, methacholine was administered to Beagle dogs (n=6) and cynomolgus monkeys (n=4) at 8 and 68 mcg/kg, respectively. A significant increase in airway resistance was observed after intravenous methacholine administration in both species (Fig. 4) with return to baseline comparable levels within 10 min. Airway resistance data analysis for individual animals revealed mean percent variations from baseline ranging from 9.5 to 18.6% for dogs and from 4.4% to 6.9% for cynomolgus monkeys, suggesting stable and reproducible assessment of lung function. Airwave oscillometry appears to be suitable for non-invasive respiratory mechanics measurements in large animal toxicity studies.

Materials and methods

Six (6) conscious Beagle dogs and 4 cynomolgus monkeys were included in the study and were acclimated to the mask on three occasions prior to measurements. Call animals connected to a forced oscillation system via a face mask for respiratory mechanics measurements:

- At baseline
- Following methacholine-induced bronchoconstriction (dogs: 8 µg/kg iv; monkeys: 68 µg/kg iv)

Animals were disconnected from the device & face mask in between measurements. High frequency waveforms applied at airway opening for 16s:

- Single frequency (19 Hz)
- Pressure and flow signals recorded during measurements.

Parameters calculated:

- Airway resistance
- Ventilation respiratory parameters (tidal volume, respiratory rate and minute ventilation)

Results

Forced oscillation technique (FOT)

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Beagle Dogs</th>
<th>Cynomolgus Monkeys</th>
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<tbody>
<tr>
<td>Cynomolgus Monkeys</td>
<td>2.45</td>
<td>13.53</td>
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<tr>
<td>Standard deviation</td>
<td>0.67</td>
<td>3.46</td>
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<tr>
<td>Group size</td>
<td>6</td>
<td>4</td>
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Discussion and conclusion

Stable and reproducible assessments of lung function were obtained in conscious Beagle dogs and cynomolgus monkeys at baseline. Significant increase in airway resistance and respiratory rate were observed in Beagle dogs and cynomolgus monkeys following methacholine administration. Changes to ventilation parameters that were observed were comparable to previous results (Authier et al, 2009) and included a significant increase in respiratory rate, tidal volume and minute ventilation in dogs while non human primates presented an increase in respiratory rate. Airwave oscillometry appears to be a suitable non-invasive methodology to enable respiratory mechanics measurements in large animal toxicity studies.

Reference


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