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PHARMACOLOGY AND TOXICOLOGY
Mini Review

Radiotelemetry Techniques for Assessment of Respiratory Function

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Abstract

Measurement of respiratory function in safety assessment has historically been reliant on restrained plethysmography procedures. Recent developments in radiotelemetry provide a means to refine this process and increase the amount of data available for evaluation of the respiratory response in animals. This review provides a summary of this technology and the data that can be collected.

Keywords: *Rip (Respiratory Inductance Plethysmography); ICH; FDA*

Introduction

Tests of pulmonary function in safety pharmacology are useful tools for evaluating the potential for compounds to produce toxicity on the pulmonary system. Insults to the pulmonary system (drugs, biologics, or toxins) can cause detectable dysfunction through multiple mechanisms. Manifestation of the response to insults will depend on the component(s) involved and the compensatory mechanism(s) initiated.

The guidance provided in the ICH S7A document [1] and the FDA Guidance for Industry [2] states respiratory safety pharmacology studies should include *respiratory rate and other measures of respiratory function (e.g. tidal volume or hemoglobin oxygen saturation)*. However, the term pulmonary function generally refers to a number of endpoint parameters of the pulmonary system from mechanical ventilation (rate, tidal volume, minute volume), to lung motion and filling (compliance, elasticity), to air movement within the tracheobronchial tree (resistance, air flow, flow durations) and finally alveolar gas diffusion all of which maintain a homeostatic balance of the dissolved gasses in the blood (PCO_2, PO_2, oxygen saturation).

In most respiratory safety pharmacology assays [3], respiratory rate, tidal volume and their mathematical product, minute volume are the primary current parameters assayed. The value of evaluating resistance and compliance as endpoints has been reviewed for the value of these parameters to characterize acute drug-induced effects on the lung, [4,5].

Radiotelemetry and Respiratory Inductance Plethysmography (RIP)

RIP utilizes straps containing inductive coils placed around the thorax and abdomen to measure lung volume changes. A continuous, low voltage electrical current is generated in the inductive coils and changes in current are produced by the expansion and contraction of the thorax and abdomen during breathingthat are proportional to the changes in length of the inductive coil straps. The RIP signals can then be linked with a radiotelemetry device for wireless transmission of the data to a receiver and associated software system for recording and analysis.

The use of RIP methodology allows for the application of more than one band, providing for the ability to assess both thoracic and abdominal movement; this then permits an assessment of phase differences between the two bands. The sinusoidal patterns produced in each band may be integrated to determine total volume inspired. The phasic relationship between the abdominal and thoracic bands may

also provide an assessment of pulmonary resistance [6]. Respiratory inductance plethysmography has been developed for clinical use, particularly in pediatric medicine [7,8,9,] and has been adapted to various species for use in preclinical drug safety assessment.

Inductive systems can measure absolute volume changes, when they have been correlated to a calibrated pneumotachograph (PNT), based on a measured difference in diameter of bands on the thoracic and abdominal regions. This system however requires calibration prior to each collection session for accuracy of the absolute measured values and completes stabilization of bands following calibration in order to maintain accuracy for the duration of a collection. These techniques require great skill and calibrations need to be carefully performed in order to generate consistent data, which could be of disadvantage if the physiological changes from an administered drug are small in magnitude.

The original designs to incorporate RIP for use in safety pharmacology studies involved the use of external bands and protective shirts/jackets linked to a radiotelemetry device that was also external. External RIP has been validated in conscious non-restrained dogs [10,11] and primates [12]. External RIP systems can be combined with cardiovascular telemetry in order to reduce the numbers of animals needed to evaluate these two systems and they can allow for 24+ hour continuous data collection. The disadvantages of the external system are the maintenance of the band placement over time, the time to place animals into the external jacket systems, particularly for primates andthe inaccuracy of the volume data that can be the result of poor calibration or animal movement, In an attempt to avoid the issues with external systems, a fully implantable system linked to radiotelemetry was developed based on trans-thoracic inductance plethysmography (TIP). The implanted telemetry device adds an impedance-based sensor and lead set for the measurement of respiratory function to the standard cardiovascular telemetry device used in large animals. Respiratory changes are detected by injecting a low amplitude and non-tissue stimulating electrical current across the thorax and measuring the induced voltage modulation via leads placed on either side of the thorax. The electrical impedance waveform can be correlated to respiratory volumewhen the measured voltage is then converted into electrical resistance. The advantage of this system is that once implanted, it cannot be displaced. However, the system placement does require knowledge of the best lead placement and surgical technique. Several labs have successfully validated these implantable systems and have found them to be valuable for respiratory assessment in dogs [13,14,15,16] and primates.

Conclusion

The goal of respiratory safety pharmacology studies under ICH S7A is to be able to predict the effects of test substances on pulmonary function by evaluating one or more parameters. The lung has limited response mechanisms that are based on the nature and duration of the insult as well as the duration for compensatory responses. A secondary goal is to refine and reduce the numbers of animals required for drug safety assessment. The advantage of the use of radiotelemetry for respiratory assessment, whether an external or implanted system, is that 1) fewer animals are required for a study, 2) longer duration measurements can be made without the limitations of plethysmography restraint, and 3) multiple repeat measurements can be made thus allowing assessment of changes associated with repeat dose administrations and can potentially be incorporated as part of a repeat dose toxicology study.

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