Regulatory Toxicology and Pharmacology 69 (2014) 135–140

Contents lists available at ScienceDirect

Regulatory Toxicology and Pharmacology

journal homepage: www.elsevier.com/locate/yrtph

Respiratory safety pharmacology – Current practice and future directions

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ARTICLE INFO

Article history:
Received 24 October 2013
Available online 23 November 2013

Keywords:
Regulatory
Methods
ICHS7A
Safety pharmacology
Respiratory
Nonclinical
PharmaPendium™

ABSTRACT

Current practice in respiratory safety pharmacology generally follows the guidance provided by the ICH document S7A and, in general, focuses on measures of pulmonary ventilation. Respiratory rate, tidal volume and/or a measure of arterial blood gases are the recommended ventilatory measurement parameters. Although these parameters will provide a measure of ventilation, other ventilatory parameters, which can provide mechanistic insight, should also be considered. Such parameters include inspiratory and expiratory times and flows and apneic time. Stimulation models involving exercise and exposure to elevated CO_2 or reduced O_2 should also be considered when enhancing measurement sensitivity or quantifying reductions in ventilatory functional reserve are desired. Although ventilatory measurements are capable of assessing the functional status of the respiratory pumping apparatus, such measurements are generally not capable of assessing the status of the other functional component of the respiratory system, namely, the gas exchange unit or lung. To characterize drug-induced effects on the gas exchange unit, measures of airway patency, lung elastic recoil and gas diffusion capacity need to be considered. Thus, a variety of methodologies and measurement endpoints are available for detecting and characterizing drug-induced respiratory dysfunction in animal models and should be considered when designing respiratory safety pharmacology studies.

1. Introduction

Safety pharmacology is a discipline within the nonclinical (preclinical) assessment of drug safety. The current practice of respiratory function assessment within safety pharmacology generally follows the regulatory guidance as stated in the ICH S7A document, which was issued in 2001. (Anon, 2001) The guidance document defines safety pharmacology studies as those that "investigate the potential undesirable pharmacodynamic effects of a test substance on physiological functions in relation to exposure in the therapeutic range and above", with test substances including new chemical entities and biotechnology-derived products for human use. The core physiological functions for evaluation include those related to the cardiovascular, respiratory and central nervous systems. These systems were selected since they represent vital functions where acute dysfunction can lead to serious adverse events. Based on the guidance provided in the ICHS7A document, current respiratory safety pharmacology studies generally focus on the measures of pulmonary ventilation. Respiratory rate, tidal volume and/or a measure of arterial blood gases are the recommended ventilatory parameters. Although these parameters will provide a measure of ventilation, other parameters, which can provide mechanistic insight, should also be considered. Furthermore, it is important to note that the respiratory system consists of two functional components – the pumping apparatus and the gas exchange unit or lung (see Fig. 1). Although ventilatory measurements are capable of assessing the functional status of the respiratory pumping apparatus, such measurements are generally not capable of assessing the status of the gas exchange unit. To characterize drug-induced effects on the gas exchange unit, measures of airway patency, lung elastic recoil and/or gas diffusion capacity need to be considered. Methods for evaluating airway resistance and lung compliance are currently available for assessing airway patency and lung elastic recoil, respectively, in animal models (Diamond and O'Donnell, 1977; Costa, 1985).

A variety of methodologies and measurement endpoints are currently available for assessing the effects of drugs on respiratory function in animal models. Because the current practice in respiratory safety pharmacology tends to focus on a limited number of respiratory parameters, the objective of this review is to discuss the value and utility of the many methodologies and measurement endpoints available to help optimize the design of respiratory safety pharmacology studies.

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http://dx.doi.org/10.1016/j.yrtph.2013.11.010

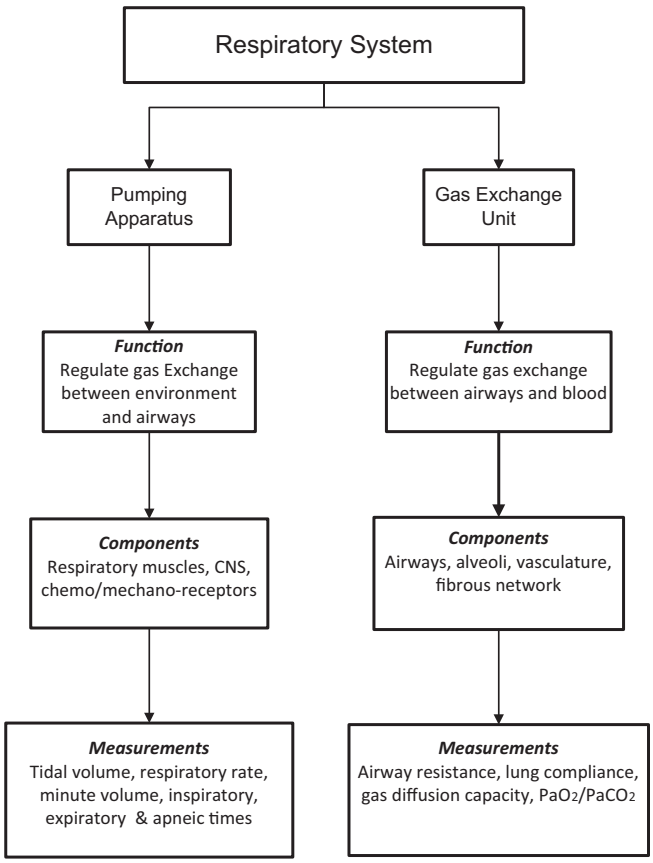

Fig. 1. A chart of the functional and structural components of the respiratory system.

2. Methodology

The methodology used to quantify the incidence of drug-induced effects on respiratory function in human clinical studies in this report involved use of the searchable database called PharmaPendium™ (Elsevier). This database contains the US Food and Drug Administration (FDA) Approval Package Database, the European Medicines Agency's (EMEA) and European Public Assessment Reports (EPARs), the Adverse Event Reporting System (AERS) reports, Meyler's Side effects of Drugs compendium and a pool of over 3000 journals and other worldwide sources. The search strategy used the sequential terms "adverse effects/toxicity (all sources)", "respiratory, thoracic and mediastinal disorders", and either "bronchial disorders (excluding neoplasms) – bronchospasm and obstruction" for identifying effects on airway resistance, the terms "respiratory disorders – breathing abnormalities" for identifying effects on ventilation and the terms "lower respiratory tract disorders (excluding obstruction and infection) – lower respiratory tract inflammation and immunologic conditions, parenchymal lung disorders (NEC) and pulmonary edema" for identifying effects on lower respiratory tract disorders. The results were then filtered for "clinical" findings and the time period of 2002–2012, to highlight the most recent findings of drug induced effects on the respiratory system. All results were transferred to Excel spreadsheets and manually checked for accuracy.

3. Evaluation of the current practice of using ventilatory endpoints alone to detect and characterize respiratory dysfunction

A question that needs to be addressed is whether or not ventilatory parameters alone can provide the endpoints necessary to evaluate drug-induced effects on the respiratory system. To address this question, the functional components of the respiratory system need to be considered (see Fig. 1). The respiratory system consists basically of two functional components – the pumping apparatus and the gas exchange unit. The function of the pumping apparatus is to regulate gas exchange between the environment and the airways to help ensure that sufficient oxygen is supplied to the circulation to meet changing metabolic demands and to remove excess carbon dioxide and other metabolic products. The components of the pump include the respiratory muscles, and the nerves, chemoreceptors and mechanoreceptors that regulate the depth and frequency of the pump. The other functional component is the gas exchange unit or lung. The function of the lung is to ensure that the gas which enters the airways is appropriately exchanged with pulmonary arterial blood. To do this, the lung must have patent airways to ensure movement of gases to the alveoli during inspiration and elastic recoil to ensure the removal of gases during expiration. The components of the gas exchange unit include the airways, alveoli, vasculature and elastic fibrous network.

Change in the functional status of the pumping apparatus is determined by measuring ventilatory patterns, which should include the endpoints respiratory rate (frequency) and tidal volume (depth). By monitoring the frequency and depth of the pumping apparatus, the effects of drugs on total pulmonary ventilation (i.e., respiratory stimulation or depression) can be established. Monitoring ventilatory parameters, however, cannot generally be used to directly assess the status of the gas exchange unit or lung. Studies that have measured drug-induced effects on both ventilatory parameters and airway resistance have demonstrated that mild to moderate (2–3-fold) changes in airway resistance do not produce changes in breathing patterns in either animal models or humans. Studies in our laboratory have demonstrated that 2–3-fold increases in airway resistance using an intravenous infusion of the bronchoconstrictive agent, methacholine, does not cause ventilatory changes in the rat, dog or monkey (unpublished results). Similar findings have been noted in humans (Savoy et al., 1984; Yasukouchi, 1992) and guinea pigs (Wiester et al., 2005). Thus, it appears that the absence of a change in ventilatory parameters cannot reliably predict the absence of mild to moderate changes in lung function. Measures of lung mechanics, which include airway resistance and lung compliance, are needed to assess airway patency and elastic recoil, respectively. Thus, to provide an assessment of drug-induced effects on both of the functional components of the respiratory system, ventilatory parameters and measures of airway resistance and lung compliance should be considered.

Changes in airway resistance and lung compliance are important safety endpoints. An increase in airway resistance can result from obstruction of the airways caused the constriction of airway smooth muscle (bronchoconstriction), hypertrophy or hyperplasia of cells lining the airways, or hypersecretion of airway mucus. An increase in airway resistance can be an acute, life-threatening event with consequences equal to that produced by ventilatory defects such as hypoventilation and respiratory failure (Hunt and Rosenow, 1992). A decrease in lung compliance can result from alterations in lower respiratory tract, which may involve changes in fibrous network, presence of interstitial or intraalveolar fluid (edema) or inflammatory cells (pneumonitis), pulmonary congestion or surfactant disruption. Although not common, acute treatment with drugs can cause pulmonary edema or pneumonitis (Erasmus et al., 2002). More importantly, in repeat dose studies where alterations in the fibrous network, surfactant disruption or pulmonary congestion are more common (Erasmus et al., 2002), measuring compliance changes could be helpful by acting as an early biomarker for detecting lower respiratory tract disorders as well as providing an understanding of functional consequences.