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Review

Optimizing the use of methods and measurement endpoints in respiratory safety pharmacology

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ABSTRACT

A variety of methods and measurement endpoints are currently available for evaluating respiratory function in animal models. To evaluate drug-induced effects on respiratory function, respiratory safety pharmacology studies generally emphasize the use of conscious animal models and measures of pulmonary ventilation. Respiratory rate, tidal volume and/or a measure of arterial blood gases are the standard measurement parameters. Although these parameters will provide a measure of ventilation, other ventilatory parameters, which can provide mechanistic insight or identify site of action, should also be considered. Such parameters include inspiratory and expiratory times, flows and pauses, 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 is 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. The objective of this review is to discuss the value and utility of the methods and measurement endpoints currently available for assessing respiratory function to help optimize the design of respiratory safety pharmacology studies.

Contents

1. Introduction

Safety pharmacology is a discipline within the nonclinical (preclinical) assessment of drug safety. A recent pharmaceutical industry survey indicates that the current practice of respiratory function assessment within safety pharmacology focuses on the use of conscious rodent models and measures of pulmonary ventilation (Lindgren et al., 2008). Conscious models help optimize respiratory function measurements by removing the depressant effect most anesthetics and analgesics have on respiratory drive (Chevillard, Megarbane, Risede, & Baud, 2009; Hirshman, McCullough, Cohen, & Weil, 1975; Nussmeier et al., 1991) and the potential alterations of response of airways to bronchoconstrictive agents (Advenier, Boissier, Mallard, & Ruff, 1978; Hirschman & Bergman, 1978). Furthermore, the duration of the experimental measurement time for anesthetized preparations is generally limited to several hours. Respiratory rate, tidal volume and derived minute volume as well as arterial blood gases are the measurement endpoints most commonly used in safety pharmacology studies

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to identify drug-induced changes in ventilation (Lindgren et al., 2008). 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 gas diffusion capacity need to be considered. Such measurement endpoints are not commonly obtained in safety pharmacology studies (Lindgren et al., 2008). Methods for evaluating airway resistance and lung compliance are currently available for use in assessing airway patency and lung elastic recoil, respectively, in animal models. Such methods are available for both anesthetized (Costa, 1985; Diamond & O'Donnell, 1977; Tobin et al., 1987) and conscious (Murphy, Renninger, & Gossett, 1998) rodent models as well as anesthetized (Black, Suki, Madwed, & Jackson, 2001; Van Scott, Aycock, Cozzi, Salleng, & Stallings, 2005) and conscious (Ingram-Ross et al., 2012; Murphy, Renninger, & Coatney, 2001) non-rodent models. Methods for evaluating lung gas diffusion capacity are also available (Kialouama et al., 2011; Qureshi, 2011).

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 methods and measurement endpoints currently available for assessing respiratory function to help optimize the design of respiratory safety pharmacology studies.

2. Use of ventilatory measurements to detect and characterize respiratory dysfunction

The respiratory system consists basically of two functional components — the pumping apparatus and the gas exchange unit (see Fig. 1). 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

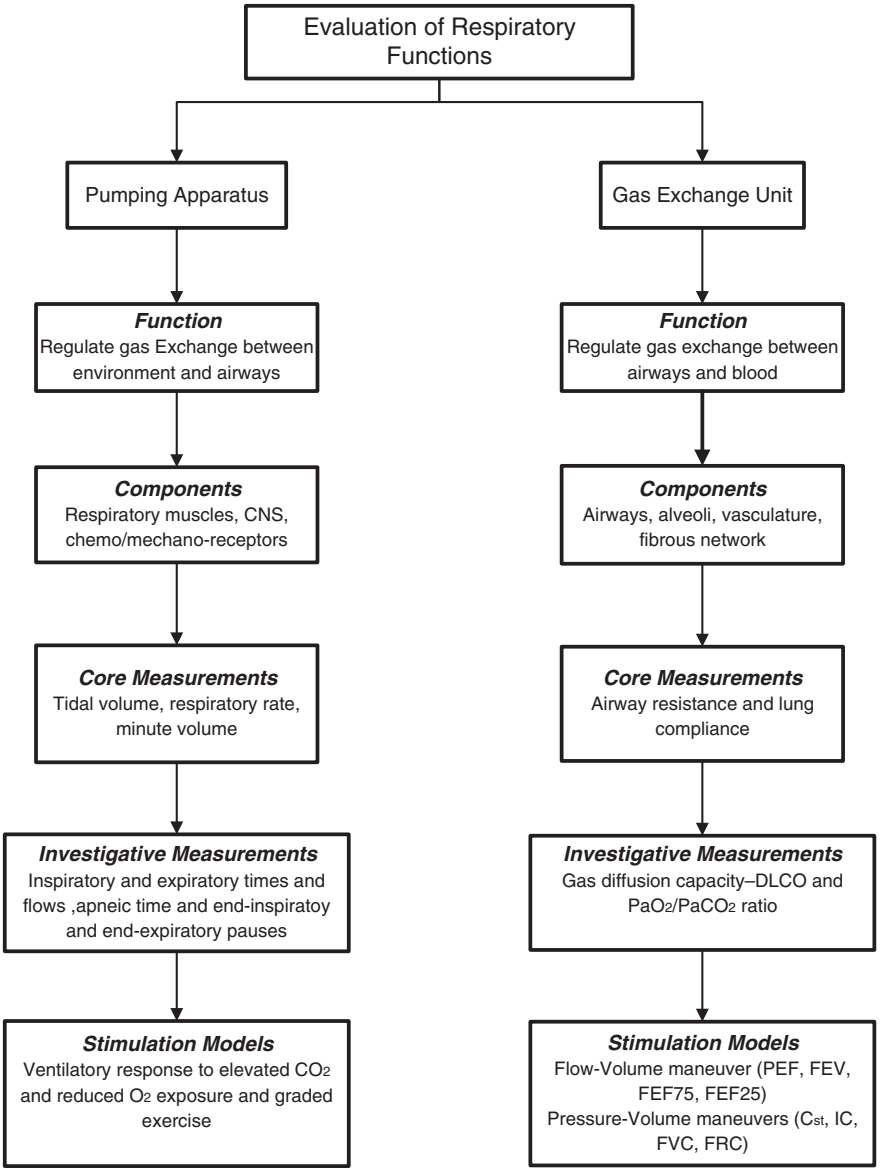

Fig. 1. A chart showing the functional and structural components of the respiratory system and the associated models and functional measurement endpoints.

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