Regulatory Toxicology and Pharmacology 81 (2016) 194–200

Contents lists available at ScienceDirect

Regulatory Toxicology and Pharmacology

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

Apneic events – A proposed new target for respiratory safety pharmacology

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ARTICLE INFO

Article history:
Received 14 December 2015
Received in revised form
30 June 2016
Accepted 2 July 2016
Available online 21 July 2016

Keywords:
Apneic event
Apnea
Intermittent hypoxia
ICHS7A
Sleep apnea
Safety pharmacology
Respiratory
Ventilatory instability
Drug safety

ABSTRACT

Current practice in respiratory safety pharmacology generally follows the regulatory guidance provided by the ICH document S7A and focuses on measures of pulmonary ventilation. What these measures do not account for is the ability of drugs to cause ventilatory instability or interruptions in ventilatory rhythm. Ventilatory instability can be identified by the presence of prolonged end-expiratory pauses or apneic periods. An apneic event has been defined as an apneic period of sufficient duration to cause hypoxia (i.e., decrease in hemoglobin oxygen saturation $\geq$ 3%). Repeated apneic events are often referred to as intermittent hypoxia. Characterizing ventilatory instability is important since (1) occurrence of apneic events in humans can lead to serious adverse outcomes such as systemic and pulmonary hypertension, cardiac arrhythmia, stroke, CNS dysfunction, metabolic disorders, enhanced tumor growth and death, (2) drugs are known to cause or exacerbate apneic events in humans, and (3) there is a preexisting condition of ventilatory instability referred to as sleep apnea that is prevalent in the human population. Evaluating this new target in respiratory safety pharmacology studies is needed to ensure that the potential for new drugs to cause or exacerbate apneic events can be identified and the impact on patient safety characterized.

1. Introduction

The International Conference on Harmonization (ICH) document S7A, which provides regulatory guidance on the conduct of safety pharmacology studies for human pharmaceuticals, currently recommends that the evaluation of drug effects on respiratory function should include the parameters respiratory rate and other measures of respiratory function (e.g., tidal volume and/or arterial blood gases) (Anon, 2001). Respiratory rate and tidal volume are commonly measured and are used to calculate minute volume, which is a measure of total pulmonary ventilation. These parameters are used primarily to assess whether a drug is a respiratory depressant or stimulant. What these parameters do not measure is the ability of drugs to cause ventilatory instability or interruptions in normal ventilatory rhythm. Ventilatory instability is detected by identifying the presence of prolonged end-expiratory pauses or apneic periods in ventilatory patterns (see Fig. 1) and is characterized by quantifying the frequency and duration of the apneic times. An apneic event has been defined by the American Academy of Sleep Medicine as an apneic period of sufficient duration to cause hypoxia, with hypoxia currently defined as a decrease in hemoglobin oxygen saturation that is equal to or greater than 3% (Berry et al., 2012). In humans, it has been determined that this degree of hypoxia is achieved with apneic times equal to or greater than 10 s (Berry et al., 2012). Repeated apneic events are often referred to as intermittent apneic events or intermittent hypoxia. The occurrence of repeated apneic events or intermittent hypoxia has been shown to be associated with a variety of adverse outcomes and a cause of increased morbidity and mortality in humans (Kohli et al., 2013; Molnar et al., 2015). Consequently, the purpose of this article is to provide evidence demonstrating the importance of apneic events as a safety target and a rationale for including apneic events as a standard safety parameter for assessing the effects of drugs on respiratory function.

2. Criteria for a new target in safety pharmacology

Safety Pharmacology is a discipline within non-clinical drug safety assessment that is responsible for identifying and characterizing the potential adverse effects of drugs on physiological

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http://dx.doi.org/10.1016/j.yrtph.2016.07.001
0273-2300/

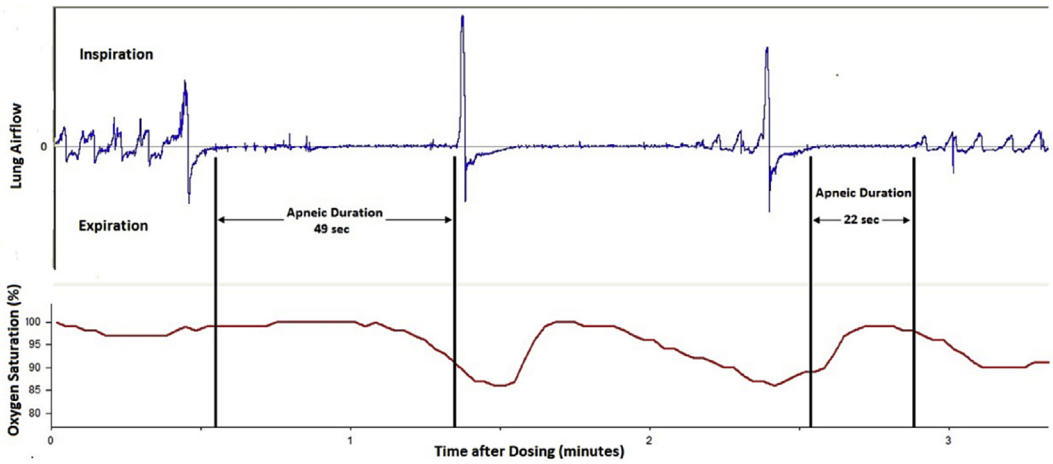

Fig. 1. Simultaneous recording of lung airflow and hemoglobin oxygen saturation from a conscious, restrained dog. Airflow was measured using a facemask with attached pneumotachograph and hemoglobin oxygen saturation monitored using a pulse oximeter. Apneic time is measured as the time from the end of expiratory flow for one breath the beginning of inspiratory flow for the succeeding breath. These prolonged apneic times were produced by an intravenous dose of the opioid agonist remifentanil. These procedures were reviewed and approved by the IACUC at GlaxoSmithKline.

functions. As such, a new target in this discipline should involve a physiological (dynamic) function and, as stated in ICHS7A, should involve "vital organ systems, the functions of which are critical for life". Based on these criteria, the respiratory, cardiovascular and nervous systems were selected as the core targets since acute functional disruption of these systems can be life threatening. Examples of such acute functional disruptions include seizures for the nervous system, cardiac arrhythmia and cardiovascular collapse for the cardiovascular system and ventilatory failure or severe bronchoconstriction for the respiratory system. An additional important requirement is that chronic alteration of the target can lead to an increased incidence of adverse outcomes. Examples of this include 2–10 mmHg increases in arterial blood pressure or 10% increases in heart rate causing an increased incidence of adverse outcomes such as stroke, ischemic heart disease, vascular damage and/or death (Singh, 2001; Prospective Studies Collaboration, 2002), chronic respiratory restrictive or obstructive disorders leading to respiratory fatigue or failure (Grassino and Macklem, 1984) and chronic drug abuse leading to adverse central nervous system outcomes such as cognitive impairment, movement disorders, depression and memory loss (Brust, 2014).

3. Justification for proposing apneic events as an important new target

Publications involving the investigation of apneic events have grown exponentially over the past 40 years (see Fig. 2). Prior to 1975 there were essentially no publications dealing with apnea, while in the past 5 years the number of new publications has grown to approximately 17 per week. This research has primarily involved characterization of the types, frequency and mechanisms of apneic events as well as investigations into the adverse outcomes associated with the repeated apneic events that occur during the sleep state. Sleep apnea is a term used to define the occurrence of apneic events during the sleep state. The sleep state is an area of medical concern since the transition from the awake to the sleep state produces a state of ventilatory instability, which includes a high susceptibility for repeated apneic events. This enhanced susceptibility to apneic events is currently believed to be due to the loss of voluntary control of breathing, reduced respiratory drive, elevated P_aCO_2 threshold for breath initiation, and a narrowing of the upper (oropharyngeal) airway (Dempsey et al., 2010). Sleep apnea is a prevalent pre-existing condition in humans being present in approximately 2–5% of adult women and 3–8% of adult men (Punjabi, 2008), with an increased incidence of 24–62% in the elderly (>65 years of age) (Ancoli-Isreal et al., 1991). Furthermore, it is estimated that 93% of women and 82% of men with moderate to severe sleep apnea are undiagnosed. (Young et al., 1997). Because of the high prevalence of sleep apnea in the general population and the fact that apneic events are associated with adverse effects, it is important for respiratory safety pharmacology studies to begin including a measure of apneic time and quantifying apneic events to determine whether new drugs have the potential to initiate apneic events or exacerbate the apneic events that occur during the sleep state.

The adverse effects of apneic events can be divided into those associated with an acute persistent disruption of ventilation and those associated with short repeated or intermittent apneic or hypoxic events. Acute persistent disruption of ventilation can be fatal and, when death occurs, these apneic events are referred to as unresolved fatal apneas. Sudden infant death syndrome (SIDS) and nocturnal respiratory failure are examples and involve suppressed ventilatory response to elevated P_aCO_2 and the loss of the sigh and gasp reflexes(Yaggi et al., 2005; Garcia et al., 2013). Sighs and gasps, which are centrally controlled (Pre-Botzinger complex), are important terminal reflexes designed to initiate arousal and activate efferent respiratory motor neurons. (Garcia et al., 2013) These severe effects fulfill the first criteria for a target in safety pharmacology by demonstrating that an acute disruption of this respiratory target can be life threatening. Repeated or intermittent apneic/hypoxic events can also lead to chronic adverse outcomes. The intermittent apneic/hypoxic events generally need to occur over a 2–8 h period per day for 14–35 days for the adverse physiological changes to become apparent in both humans (Cutler et al., 2004; Tamisier et al., 2011) and animals models (Prabhakar and Kumar, 2010; Olea et al., 2014; Souza et al., 2015). Adverse outcomes associated with intermittent apneic/hypoxic events during the sleep state include systemic (Tamisier et al., 2011; Prabhakar and Kumar, 2010; Souza et al., 2015) and pulmonary (Nattie and Doble, 1984; Thomas and Wanstall, 2003) hypertension, cardiac arrhythmia (Becker et al., 1998; Benjamin and Lewis, 2008), stroke (Shahar et al., 2001; Yaggi et al., 2005), heart failure (Benjamin and Lewis, 2008; Shahar et al., 2001), cardiovascular related death (Yaggi et al., 2005; Martinez-Garcia et al., 2012; Gami et al., 2005),