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Review

Respiratory stimulant drugs in the post-operative setting☆☆

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ABSTRACT

Drug-induced respiratory depression (DIRD) is a common problem encountered post-operatively and can persist for days after surgery. It is not always possible to predict the timing or severity of DIRD due to the number of contributing factors. A safe and effective respiratory stimulant could improve patient care by avoiding the use of reversal agents (e.g., naloxone, which reverses analgesia as well as respiratory depression) thereby permitting better pain management by enabling the use of higher doses of analgesics, facilitate weaning from prolonged ventilation, and ameliorate sleep-disordered breathing peri-operatively. The purpose of this review is to discuss the current pharmaceutical armamentarium of drugs (doxapram and almitrine) that are licensed for use in humans as respiratory stimulants and that could be used to reverse drug-induced respiratory depression in the post-operative period. We also discuss new chemical entities (AMPAkines and GAL-021) that have been recently evaluated in Phase 1 clinical trials and where the initial regulatory registration would be as a respiratory stimulant.

1. Introduction

Respiratory depression in the hospital setting is a common problem encountered post-operatively and in the intensive care unit (Overdyk et al., 2007). In many instances, the respiratory depression is an undesired consequence of administering drugs that sedate or relieve pain. To illustrate, among postoperative patients receiving opioids, the incidence of clinically significant respiratory depression (respiratory acidosis and hypoxemia) requiring intervention occurs in approximately 2% of the surgical population (Overdyk et al., 2007; Shapiro et al., 2005). Unfortunately, it is not always possible to predict the timing or severity of these events due to the number of contributing factors, including age, sex, body-mass index, presence of co-morbidities, and concomitant medications administered. On the other hand, some risk factors are very strong predictors of respiratory complications post-operatively. For example, in bariatric patients the incidence of deleterious respiratory events post-operatively may be as high as 100% (Overdyk et al., 2007).

Typically, in the immediate post-operative period and while in the post-anesthesia care unit, a patient's ventilatory performance is monitored intensively and respiratory depression can be treated early with interventions such as verbal stimulation, oxygen therapy, and positive airway pressure (i.e., CPAP). Occasionally, profound respiratory depression requires reversal by administering a selective antagonist of (e.g., naloxone or flumazenil) and/or decreasing subsequent doses of the depressant agent. Although this approach may improve respiratory function, sedation and/or analgesia will be sub-optimal. If a safe and effective respiratory stimulant drug were available to support breathing post-operatively it is likely that pain control in some patients would improve because analgesia could be used as the endpoint for titration of an opioid rather than the magnitude of respiratory depression it elicits.

For those patients who remain intubated following surgery (e.g., open chest procedures), mechanical ventilation avoids acute post-operative respiratory depression, but creates the need for weaning from mechanical ventilation and subsequent extubation, and overall increases pulmonary complications. Early weaning and extubation is associated with decreased post-operative morbidity and mortality, however, not all patients are able to successfully wean from the ventilator and maintain adequate ventilation after extubation, creating a clinical situation requiring an urgent response, including re-intubation. In this scenario, acute ventilatory support with a ventilatory stimulant drug would likely provide substantial patient benefit and hasten patient return to an observational ward.

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Patients who are housed on usual patient floors for routine post-operative care are at greatest risk for opioid-induced respiratory depression from postoperative day 1 through day 5 (Overdyk et al., 2007; Reeder et al., 1992a,b; Taylor et al., 2005). In this setting, respiratory monitoring is typically limited. Progressive and ultimately life-threatening respiratory events may go unrecognized until significant morbidity or mortality occurs. Thus, there is a need for a respiratory stimulant beyond the post-anesthesia care unit. This requirement could be met by a drug that is formulated as: (1) both an intravenous and oral preparation, or (2) an intravenous product with a long duration of effect.

Another important risk factor that is increasing in prevalence is the co-morbidity of sleep-disordered breathing in the peri-operative patient (Vasu et al., 2012). Unfortunately, the majority of patients with sleep-disordered breathing remain undiagnosed and opioids and other respiratory depressants can exacerbate this condition (Yue and Guilleminault, 2010; Zutler and Holty, 2011). Furthermore, opioids may have increased potency as analgesics in pediatric and adult patients with nocturnal hypoxemia due to sleep apnea (Brown et al., 2006; Doufas et al., 2013). This also translates into increased potency as respiratory depressants (Waters et al., 2002), creating a vicious circle of cause and effect. The importance of sleep-disordered breathing peri-operatively dictates that any drug developed for use as a respiratory stimulant needs to have efficacy in sleep-related breathing disturbances or, at the very least, not exacerbate the disorder.

The purpose of this review is to discuss the current pharmaceutical armamentarium of drugs that are licensed for use in humans as respiratory stimulants and that could be used to reverse drug-induced respiratory depression in the post-operative period. These are currently restricted to doxapram (globally) and almitrine (select countries). Both drugs are believed to increase minute volume primarily by inhibiting potassium channels within the carotid bodies. Thus, we will begin with a short description of the role of potassium channels in carotid body chemoreception and the effects of these drugs at this molecular target. We will then review the past and present use of doxapram and almitrine and their limitations as chemotherapeutics. We will also briefly discuss new chemical entities (AMPAkines and GAL-021) that have recently been evaluated in Phase 1 clinical trials and where the initial regulatory registration would likely be as a respiratory stimulant in the post-operative setting.

2. Carotid body effects of current drugs

Doxapram and almitrine stimulate breathing by acting at the level of the carotid bodies. Transecting the carotid sinus nerve blocks the ventilatory effects of almitrine at all doses tested and doxapram at normal clinical doses (de Backer et al., 1983; De Backer et al., 1985; Laubie and Schmitt, 1980; Mitchell and Herbert, 1975; Nishino et al., 1982). At higher doses of doxapram, residual ventilatory stimulation persists in carotid and aortic denervated animals, indicating an additional site of action exists presumably within the central nervous system (CNS) (Mitchell and Herbert, 1975; Wilkinson et al., 2010).

Both drugs are believed to increase carotid sinus nerve activity by co-opting a mechanism that contributes to endogenous hypoxia sensing, namely inhibition of potassium channels on glomus cells. A detailed description this mechanism can be found elsewhere (Buckler, 2007; Peers et al., 2010). In brief, hypoxia inhibits K^+ channels on type I glomus cells causing depolarization of the cell membrane and an influx of Ca^{2+} through voltage-gated Ca^{2+} channels. Calcium influx triggers exocytosis of excitatory neurotransmitters (e.g., ATP and acetylcholine), which in turn generate action potentials on nearby carotid sinus nerve afferent terminals. Of the myriad oxygen-sensitive K^+ channels that exist, the primary types expressed on human glomus cells are a voltage-dependent and Ca^{2+}-activated channel (IKCa, also known as BK) and a background leak channel (TWIK-related acid-sensitive K^+ channel; TASK) (Fagerlund et al., 2010; Mkrtchian et al., 2012). The main function of BK channels is to contribute to action potential repolarization (Sah, 1996). Thus, drug-induced inhibition of this channel increases action potential frequency. TASK channels are outward leak currents that maintain resting membrane potential (Mathie and Veale, 2007). Inhibition of these channels increases cell excitability.

The effects of doxapram on BK channels were initially evaluated using isolated neonatal rat glomus cells (Peers, 1991). In this study, doxapram reversibly inhibited BK current ($IC_{50} \sim 5\ \mu M$). In a later study using isolated rabbit carotid bodies, BK and TASK channel openers blocked the effects of doxapram on carotid sinus nerve activity, suggesting that TASK channel inhibition also contribute to the ventilatory effects of doxapram (Takahashi et al., 2005). Indeed, doxapram inhibits current through cloned rat TASK channels expressed in oocytes ($IC_{50} \sim 400$ nM for the TASK-1 subtype) (Cotten et al., 2006). Given that therapeutic plasma concentration of doxapram is in the order of 4–5 μM (see below), these studies suggest that doxapram may increase ventilatory drive via inhibition of TASK channels and to a lesser extent the BK channel.

The effects of almitrine on ionic currents from isolated rat type 1 glomus cells have been reported (Lopez-Lopez et al., 1998; Peers and O'Donnell, 1990). Almitrine inhibits BK currents ($IC_{50} \sim 200$ nM) without altering voltage dependent K^+, Na^+, or calcium currents. To our knowledge, the effect of almitrine on TASK channels has not been tested.

3. Doxapram

3.1. General use

Doxapram was first identified as an analeptic agent with ventilatory stimulant properties in the 1960s (Ward and Franko, 1962) and was used clinically for more than 40 years. In recent years, the use of doxapram has declined considerably due to its side-effect profile that includes hypertension, anxiogenesis, and dyspnea (see below). Doxapram (Dopram®) is still licensed for human use with three primary indications (as per the Dopram package insert, FDA.gov, 2013): (1) to stimulate respiration in the postoperative patient and in patients with drug-induced post-anesthesia respiratory depression or apnea, (2) to stimulate respiration, hasten arousal, and return airway protective reflexes in patients with respiratory and CNS depression due to drug overdosage, and (3) to stimulate respiration in chronic pulmonary disease patients with acute respiratory insufficiency. Doxapram also is used off-label to decrease post-operative shivering in adults (Singh et al., 1993), though this effect may be minimal (Komatsu et al., 2005), and apnea of prematurity in human neonates (Bairam et al., 1992).

In veterinary medicine, doxapram is licensed for use in dogs, cats and horses (Dopram-V®, Respiram®), and is used off-license in other species. In animals, doxapram is primarily used to stimulate respiration and speed awakening after general anesthesia, diagnose laryngeal paralysis, and initiate and stimulate respiration in neonates following cesarean section or dystocia. However, in both human and veterinary medicine, the need for an analeptic to hasten arousal from anesthesia has declined considerably because of the introduction of shorter-acting anesthetic agents (e.g., sevoflurane and propofol).

3.2. Effects on breathing

3.2.1. Effects on ventilation in drug-naïve subjects

Doxapram elicits respiratory stimulation as evidenced by increased minute volume ($\dot{V}_E$) in a broad range of species (Bairam et al., 1990; Bleul et al., 2010; Bleul and Bylang, 2012; Burki, 1984; Calverley et al., 1983; Forster et al., 1976; Gregoretti and Pleuvry, 1977; Khanna and Pleuvry, 1978; Murphy et al., 2010; Wilkinson et al., 2010). The increase in $\dot{V}_E$ is predominantly due to an increase in tidal volume (V_T) with little effect on respiratory rate (RR), although a few studies report an increase in both. The effective blood concentration of doxapram in humans to increase $\dot{V}_E$ is 1.5–2 μg/mL or ~4–5 μM (Calverley et al., 1983). This is similar to rats (Galleon Pharmaceuticals, unpublished data) and is likely conserved across species. The major metabolite, keto-doxapram, is also a ventilatory stimulant albeit with lower potency than the parent compound (Bairam et al., 1990).

3.2.2. Effects on drug-induced hypoventilation

Many classes of drugs administered in the perio-operative setting elicit alveolar hypoventilation. Doxapram can normalize ventilation by increasing ventilatory drive (i.e., a left shift in the CO_2 response curve) (Ramamurthy et al., 1975; Randall et al., 1989), and increasing CO_2 (i.e., increased slope of the CO_2 response curve) and hypoxic (Lugliani et al., 1979) chemosensitivity. As long as a patient can respond to chemoreceptor stimulation, doxapram should be able to increase $\dot{V}_E$ in the presence of most drugs. Situations where a patient may not respond include severe CNS depression (e.g., due to prolonged hypoxia, major drug overdose, or brainstem injury), or an inability to increase activity of the respiratory muscles (e.g., in the presence of muscle relaxants or neuromuscular disorders).

The class of drug most often associated with acute life-threatening respiratory depression is the opioids. Doxapram diminishes the magnitude of opioid-induced hypoventilation across a range of species (Franko and Ward, 1971; Gasser, 1977; Golder et al., 2012c; Gregoretti and Pleuvry, 1977; Hillidge, 1976; Khanna and Pleuvry, 1978; Ramamurthy et al., 1975) (Fig. 1). Naloxone, a selective opioid receptor antagonist, reverses opioid-induced respiratory depression but also removes analgesia which creates a clinical problem post-operatively. Doxapram does not interact with opioid receptors and so analgesia is maintained.

3.2.3. Effects on sleep-disordered breathing

Opioids and other respiratory depressants exacerbate preexisting SDB in the perio-operative period (Vasu et al., 2012). The effect of doxapram on the severity of obstructive sleep apnea (OSA) has been evaluated in a small study using four subjects (Suratt et al., 1986). Doxapram decreased the duration and severity of oxyhemoglobin desaturation events, with no effect on the number of desaturations or time spent in NREM and REM sleep. Unfortunately, doxapram also increased blood pressure, which is undesirable in people with a disease known to cause hypertension. Although the small sample size diminishes the findings of this study, the data suggest that increasing respiratory drive chemically, presumably via peripheral chemoreceptors, is a rational approach to treating sleep disordered breathing (SDB) in the perio-operative setting.

3.3. Side effect profile and toxicity

Nowadays, the primary limitation to more widespread use of doxapram is its analeptic effect. Previously, this property was desirable and used to hasten recovery from anesthesia. With use of shorter-acting anesthetic agents, the need for stimulants has diminished and the analeptic properties of doxapram are more evident.

Doxapram is panicogenic and patients with a panic disorder exhibit increased sensitivity to doxapram (Abelson et al., 1996a,b). Panic disorders and abrupt increases in arousal can elicit hyperventilation (Nardi et al., 2009). This relationship may explain why residual ventilatory stimulation persists following doxapram administration in carotid denervated/ablated animals and humans.

The pressor effects of doxapram have been recognized since its initial use. In humans and dogs, the pressor effect in normotensive individuals has been described as “slight” with a larger sustained increase in blood pressure and cardiac output documented in hypotensive individuals (Kim et al., 1971; Stephen and Talton, 1964). The mechanism whereby doxapram increases blood pressure is unknown but may be related to increased circulating catecholamine levels during administration (Abelson et al., 1996b).

Doxapram increases heart rate in multiple species (Gay et al., 1978; Jensen and Klemm, 1967; Wernette et al., 1986). The effects on cardiac rhythm are less consistent (Huffington and Craythorne, 1966; Stephen and Talton, 1966). Doxapram prolongs the QT interval on electrocardiograms in premature infants by an unknown mechanism (Miyata et al., 2007). Drug-induced prolongation of the

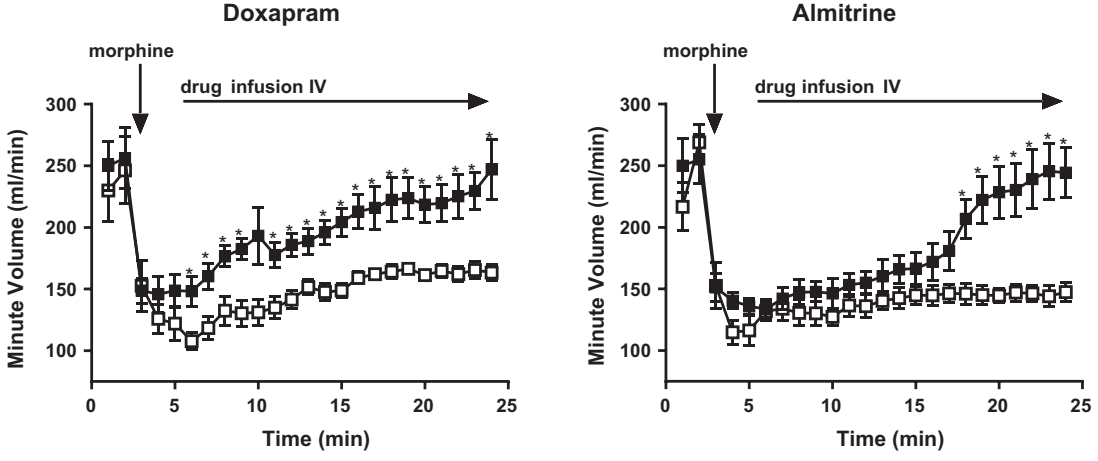

Fig. 1. The effects of doxapram and almitrine on morphine-induce respiratory depression in conscious rats. Minute volume was measured using whole-body plethysmography before and after morphine (10 mg/kg IV) bolus and doxapram (1.0 mg/kg/min IV) and almitrine (0.03 mg/kg/min) infusion. Morphine decreased minute volume approximately 40–50% below baseline values. Subsequent doxapram and almitrine infusion significantly increased minute volume compared to vehicle controls. Graphs are modified from those previously presented in poster format (Golder et al., 2012c; Gruber et al., 2011). *Different to vehicle, $p < 0.05$. Values are means ± SEM.

QT interval may be followed by potentially fatal arrhythmias, such as Torsade de pointes.

In terms of severe life-threatening side effects, doxapram is described as having a wide therapeutic window (in humans ~20–40 fold) (Yost, 2006). At toxic single doses in animals (e.g., rat LD_{50} = 72 mg/kg IV), the primary manifestation of toxicity is CNS excitation including hyperactivity, tremors, tonic–clonic movements, and convulsions (Ward et al., 1968). Other symptoms include salivation, diarrhea, emesis, urination, and defecation (Ward et al., 1968). Doxapram is pro-convulsant but only at doses much higher than those that evoke respiratory stimulation (Albertson et al., 1983).

3.4. Stereo-selective effects of doxapram

Doxapram is racemic, and exists as a racemate with positive (+) and negative (−) enantiomers. There is considerable precedent in the literature for the pharmacokinetic and pharmacodynamic properties of chiral drugs to be stereoselective. In these instances the enantiomer possessing the desirable pharmacological properties is termed the eutomer, whereas the enantiomer lacking such properties is termed the distomer. We hypothesized that the respiratory stimulant properties of doxapram would be stereoselective and could be evaluated by chirally separating doxapram into its (+) enantiomer (GAL-054) and (−) enantiomer (GAL-053). Pre-clinically we demonstrated that the (+) enantiomer, GAL-054, and not the (−) enantiomer, GAL-053, dose-dependently increased minute volume when administered intravenously to drug naïve and opioid challenged rats and cynomolgus monkeys (Golder et al., 2012a,b,c). Moreover, the deleterious side-effects of agitation and seizures were restricted to GAL-053. There were minimal behavioral changes observed in rats and monkeys receiving GAL-054. Thus, GAL-054 is the eutomer and GAL-053 the distomer of doxapram. Unfortunately, in conscious rats GAL-054 increased blood pressure approximately 15–20% above baseline values at doses that were moderately respiratory stimulant. This effect was confirmed in a Phase 1 clinical trial evaluating the effects of GAL-054 in healthy volunteers (Galleon Pharmaceuticals, unpublished data). Thus, the ventilatory stimulant and pressor effects of doxapram cannot be separated by enantiomeric separation of the racemate.

4. Almitrine

4.1. General use

Almitrine bismesylate was developed in the 1970s as a respiratory stimulant and first commercialized in 1984 when it was marketed under the product name Vectarion™ (Tweney and Howard, 1987). In the past, almitrine was used intravenously in the peri-operative setting for indications mirroring those for doxapram, except not as an analeptic agent. Nowadays, albeit with declining frequency, almitrine is used chronically in the management of chronic obstructive pulmonary disease (COPD) (Howard, 1984; Smith et al., 1987; Tweney, 1987; Tweney and Howard, 1987).

Almitrine has never been licensed for use in the United States. In the European Union, availability is limited to France, Poland and Portugal, where its primary indication is to improve oxygenation in patients with chronic obstructive pulmonary disease. The European Medicines Agency has started a review of almitrine related to adverse side effects including weight loss and peripheral neuropathies.

4.2. Effects on breathing

4.2.1. Effects on ventilation

Almitrine increases $\dot{V}_E$ by increasing V_T and/or RR across multiple species (Dhillon and Barer, 1982; Flandrois and Guerin, 1980; MacLeod et al., 1983; O'Halloran et al., 1996; Saupe et al., 1992; Weese-Mayer et al., 1986, 1988). Almitrine is also efficacious in the face of an opioid challenge (Fig. 1) (Gruber et al., 2011). As discussed above, the effects of almitrine on breathing are solely due to stimulation of the peripheral chemoreceptors. Only one of almitrine's metabolites is active, but its potency as a respiratory stimulant is 5 times less than the parent compound (Campbell et al., 1983).

Almitrine improves post-operative indices of ventilation while causing a mild decrease in blood pressure and no change in heart rate or cardiac output (Laxenaire et al., 1986; Parotte et al., 1980), contrasting with the pressor effects of doxapram. Almitrine's primary use is as a respiratory stimulant in people with COPD. Almitrine increases ventilation in patients with COPD, significantly improving blood gases and reducing the incidence of intubation when compared to placebo controls (Lambropoulos et al., 1986).

4.2.2. Effects on breathing control at sub-stimulatory dose

At doses that do not increase $\dot{V}_E$, almitrine is still capable of altering breathing control. This is best illustrated by a study where the effects of gradually increasing the dose of almitrine on hypoxic and hypercapnic sensitivity were evaluated in healthy volunteers (Stanley et al., 1983). Almitrine dose-dependently increased the slopes of the hypoxic (at >50 ng/mL) and hypercapnic (at >200 ng/mL) ventilatory responses without increasing $\dot{V}_E$ on room air. The authors also noted that the effects of almitrine on chemosensitivity persisted despite plasma levels of the drug declining below these thresholds. Small increases in $\dot{V}_E$ (~11% above baseline) on room air were only observed when plasma concentrations of almitrine exceeded approximately 250 ng/mL. The ability of a carotid body stimulant to increase chemosensitivity without an accompanying increase in $\dot{V}_E$ during normoxia may reflect the limited role of the carotid body in modulating $\dot{V}_E$ during normoxic conditions. Thus, potentiation of carotid body signaling in this scenario may only be evident when an individual is exposed to hypoxia and/or hypercapnia. The persistent effect of almitrine on chemosensitivity despite waning plasma levels may be due to the presence of an active metabolite or tissue binding of the drug within the peripheral chemoreceptors.

4.2.3. Effects on sleep disordered breathing

The effects of almitrine on sleep-disordered breathing in humans have been evaluated with equivocal results (Hackett et al., 1987; Mangin et al., 1983). Carotid body stimulation can stabilize breathing and decrease apneic events during sleep by increasing minute volume, thereby decreasing loop gain (Dempsey et al., 2012). Loop gain is an engineering term that describes the sensitivity of a variable system to perturbations. Loop gain comprises controller gain (i.e., chemoreceptors) and plant gain (i.e., the blood gas response to a change in ventilation). Almitrine has been evaluated in an animal model where the influence of loop gain on ventilatory stability is measured (Nakayama, 2002). Almitrine decreased plant gain by stimulating ventilation and was able to protect against ventilator-induced central apneas and hypopneas. Countering this stabilizing influence is the effect of almitrine on hypoxic chemosensitivity (i.e., controller gain). Thus, almitrine can increase controller gain, which would worsen sleep-disordered breathing. The net effect of almitrine on sleep-disordered breathing is likely to be dependent on the dose administered and the type of patient in question.

4.2.4. Effects on ventilation–perfusion matching

Almitrine exerts beneficial effects on pulmonary gas exchange (increased PaO_2, and improved ventilation–perfusion ratios – $\dot{V}_A/\dot{V}_Q$ matching) without increasing $\dot{V}_E$ (Barer et al., 1983; Hughes et al., 1983, 1986; Melot et al., 1989). The mechanism responsible for this effect is believed to be enhanced hypoxic pulmonary vasoconstriction (HPV). Almitrine improves $\dot{V}_A/\dot{V}_Q$ matching in patients with COPD and increases pulmonary vascular resistance consistent with an effect on pulmonary vascular tone (Melot et al., 1983a,b). HPV is often depressed peri-operatively, so any new drug for this setting that normalizes HPV would be highly desirable.

4.3. Side effects and toxicity

Almitrine has a lower therapeutic dose and greater toxic dose than doxapram (almitrine $LD_{50} > 200$ mg/kg in mice *cf.* doxapram LD_{50} of 85 mg/kg in mice). Acutely, almitrine is generally well tolerated and safe in humans. Not surprisingly, increased awareness of breathing and breathlessness are the most common side-effects following almitrine administration (Marsac, 1986; Naeije et al., 1981). Other side effects included headache, fatigue, insomnia, malaise, flushing, sweating, and postural dizziness (Naeije et al., 1981; Sergysels et al., 1980). Gastro-intestinal side effects included nausea, abdominal discomfort, and diarrhea (MacLeod et al., 1983). There are minimal changes in cardiovascular parameters except for a mild increase in pulmonary artery pressure (Gluskowski et al., 1984, 1985; MacNee et al., 1986).

Almitrine is less tolerated when administered chronically. Multi-year trials observed that patients receiving almitrine exhibited significant weight loss (>15%) that appeared to be anorectic in nature (Ansquer, 1985; Ansquer et al., 1985; Gherardi et al., 1989). The most significant and consistent side effect of chronic (more than 3 months) almitrine administration is peripheral neuropathy (Allen, 1988; Allen and Prowse, 1989; Bouche et al., 1989; Gherardi et al., 1989; Suggett et al., 1985). Further examination revealed that these patients showed axonal degradation and a decrease in the density of large myelinated fibers. Mechanistic studies in animals identified the detriazinyl metabolite, 4,4′-fluorobenzhydrylpiperazine, the major almitrine metabolite formed in humans, as the probable cause of the evoked neuropathy (Yamanaka et al., 1997). Thus, the use of almitrine is no longer recommended and is withdrawn or in regulatory review in many countries.

5. New drugs in development as respiratory stimulants

There have been only a few new therapeutic agents developed that focus on respiratory control and even fewer have been approved for clinical use during the previous decades. One issue has been poor translation of pre-clinical efficacy into humans, as has occurred with the 5-$HT1_A$ and 5-HT_4 receptors agonists, buspirone and mosapride (Lotsch et al., 2005; Oertel et al., 2007). This may be more about the targets selected and not related to the use of rodents as models for drug-induced respiratory depression, given the initial success and translatability of the AMPAkines and GAL-021 (see below).

The paucity of the new molecule entities in respiratory modulation has resulted in the route to and benchmarks for registering new therapeutic products to be absent, outdated, or limited to single pharmacological mechanism action. Thus, the methods for determining an early clinical Proof-of-Concept trial, including the selection of meaningful endpoints, will need to be developed for each potential indication that has strong negative predictive value balanced by good positive predictive value for the therapeutic utility of potential agents. Overall, much effort will be required by health authorities, medical subspecialists, and drug developers to establish the pathway to new therapeutic entities marketing approval and available for practitioners.

5.1. AMPAkines

AMPAkines are modulators of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors and have been widely explored for a variety of neuropsychiatric diseases including schizophrenia and epilepsy (Chang et al., 2012; Russo et al., 2012). Cognitive improvement has been the primary focus of most research with this drug class (Hamlyn et al., 2009). Glutamate acting via AMPA receptors is essential for maintaining respiratory rhythmogenesis at the purported kernel of rhythm generation, the preBötzinger complex in the hindbrain (Funk et al., 1993; Greer et al., 1991). Thus, the rationale for the use of AMPAkines to treat respiratory depression, in particular the type caused primarily by a decrease in respiratory rate (e.g., opioid-induced respiratory depression), is that positive allosteric modulators of AMPA receptors would enhance respiratory rhythm.

Various AMPAkines (Cortex Pharmaceuticals, Inc.) have been evaluated preclinically and clinically as respiratory stimulants. The positive AMPA allosteric modulator CX546 reversed the ventilatory suppressive effects of fentanyl and phenobarbital in the rat (Ren et al., 2006). A second AMPA receptor modulator, CX717, has been tested pre-clinically and is also able to reverse the respiratory depressive effects of fentanyl, alcohol and pentobarbital (Ren et al., 2009, 2012). CX717 also reverses opiate suppression of hypoglossal motor neurons (Lorier et al., 2010). In young healthy subjects with a target alfentanil infusion concentration of 100 ng/mL (i.e., analgesic), CX717 prevented the fall in respiratory rate vs. placebo (Oertel et al., 2010). However, in that study there also was an interaction between alfentanil and CX717 with respect to visual analog scale parameter "tiredness", in that the participants receiving CX717 reported increased tiredness compared to placebo controls.

In humans, AMPAkines improved memory and information processing in the healthy elderly (Wezenberg et al., 2007) and people with schizophrenia (Goff et al., 2008). In a randomized, double-blind, crossover study in sleep deprived young subjects, CX717 enhanced cognitive performance and alertness (Boyle et al., 2012). Slow wave sleep was reduced and recovery sleep impaired. Thus, the respiratory stimulatory effects of new AMPAkine molecules are associated with stimulatory neuropsychiatric effects on arousal-alertness state and cognitive performance. It remains possible that dual effects of a single molecule on the neuropsychiatric and respiratory systems will limit the utility of these compounds as respiratory stimulants.

5.2. GAL-021

Agents that increase the drive to breathe by mimicking the effects of acute hypoxia and/or hypercapnia at the level of the peripheral chemoreceptors represent a rational approach toward the development of therapeutics for breathing control disorders that would benefit from ventilatory stimulation. GAL-021 (Galleon Pharmaceuticals, Inc.), a BK channel blocker, is currently in early clinical trials. GAL-021 is a new chemical entity designed based on our understanding of the structure–activity relationship and structure-tolerability limitations of almitrine. GAL-021 does not contain the fluorinated piperazine ring, which causes lipidosis in dorsal root ganglia in rat leading to peripheral neuropathy and hindlimb dysfunction (Yamanaka et al., 1997). GAL-021 was extensively profiled in mice, rats, dogs, and cynomolgus monkeys preclinically. In brief, GAL-021 stimulates ventilation and attenuates opiate-induced respiratory depression but not

morphine analgesia (Baby et al., 2012a; Golder et al., 2012d). GAL-021 also reverses drug-induced respiratory depression elicited by isoflurane, propofol, and midazolam (Galleon Pharmaceuticals, unpublished data). Ventilatory stimulation is accompanied by enhanced carotid sinus nerve afferent and phrenic nerve efferent activity (Baby et al., 2012b). Carotid sinus nerve transection almost completely abolishes (~85% reduction) GAL-021-induced respiratory stimulation (Baby et al., 2012b). The residual stimulation was blocked when the cervical vagi were transected in addition to the carotid sinus nerve (Galleon Pharmaceuticals, unpublished data). Thus, some of the effects of GAL-021 on ventilation are mediated from other peripheral sites, most likely aortic chemoreceptors.

In healthy human subjects, GAL-021 administration caused statistically significant increases in $\dot{V}_E$ ($AUE_{0-1\,h}$) with reciprocal suppression of $ETCO_2$ during 1-h continuous infusions. The half-maximal effect on $\dot{V}_E$ and $ETCO_2$ occurred rapidly (<10 min). Drug concentration rose rapidly during the infusion and declined rapidly initially with a distribution $t_{1/2}$ of 30 min and then more slowly with a terminal $t_{1/2}$ of 5–7 h. Thus, in humans GAL-021 has pharmacodynamic and pharmacokinetic characteristics consistent with an acute care medication. A Proof-of-Concept study using opioids in a hypercapnic clamp setting is on-going in humans to determine the clinical utility of GAL-021 and to validate the BK channel as a therapeutic target. Further clinical development with phase 2 studies in patients with post-operative respiratory depression is planned for late 2014.

6. Conclusions

It is clear that there is an unmet medical need for a safe and effective respiratory stimulant, especially during sleep, in post-operative patients receiving potent respiratory depressants. Doxapram and almitrine illustrates the potential utility of a carotid body stimulant in the treatment of drug-induced respiratory depression, and possibly exacerbated sleep disordered breathing in the perioperative setting. However, the widespread use of both drugs is limited by their side effect profiles and toxicities. In the case of doxapram, the primary limitation is in its pressor effects. But is a pressor effect an inherent property of a carotid body stimulant? In a recent review, Kumar suggests that the answer is no (Kumar, 2009). He argues that although carotid body stimulation elicits a stereotypical systemic response, which includes a range of cardiovascular reflexes, the precise cardiovascular effect depends upon whether ventilation is, or is not, controlled. For example, if ventilation can increase (e.g., a spontaneously breathing patient), carotid body stimulation typically increases heart rate and decreases systemic vascular resistance with minimal changes or a slight decrease in blood pressure. On the other hand, if ventilation is controlled (i.e., a patient on a ventilator), carotid body stimulation usually causes bradycardia, an increase in vascular resistance, and an associated pressor effect. This dependence on whether breathing is spontaneous or controlled may be related to the interplay of pulmonary vagal afferent feedback and $PaCO_2$ on cardiovascular regulation. We have found that doxapram increases blood pressure in carotid body denervated rats (Galleon Pharmaceuticals, unpublished data) suggesting that the pressor effects of this compound are due, at least in part, to mechanisms outside of the carotid bodies. Thus, a selective carotid body stimulant with minimal central effects is likely to be better tolerated in the post-operative setting than doxapram. This is evident in the case of almitrine. Almitrine has a myriad of effects that would be beneficial post-operatively, including reversal of drug-induced hypoventilation, enhanced chemosensitivity, decreased plant gain, and improved $\dot{V}_A/\dot{V}_Q$ matching, but with minimal pressor effects. The primary limitation with almitrine is the peripheral neuropathy following chronic use. GAL-021 does not contain the fluorinated piperazine ring associated with this toxicity and appears to retain many of the desirable properties of almitrine.

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