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Averting Opioid-induced Respiratory Depression without Affecting Analgesia

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ABSTRACT

The ventilatory control system is highly vulnerable to exogenous administered opioid analgesics. Particularly respiratory depression is a potentially lethal complication that may occur when opioids are overdosed or consumed in combination with other depressants such as sleep medication or alcohol. Fatalities occur in acute and chronic pain patients on opioid therapy and individuals that abuse prescription or illicit opioids for their hedonistic pleasure. One important strategy to mitigate opioid-induced respiratory depression is cotreatment with nonopioid respiratory stimulants. Effective stimulants prevent respiratory depression without affecting the analgesic opioid response. Several pharmaceutical classes of nonopioid respiratory stimulants are currently under investigation. The majority acts at sites within the brainstem respiratory network including drugs that act at α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (ampakines), 5-hydroxytryptamine receptor agonists, phospodiesterase-4 inhibitors, D_1-dopamine receptor agonists, the endogenous peptide glycyl-glutamine, and thyrotropin-releasing hormone. Others act peripherally at potassium channels expressed on oxygen-sensing cells of the carotid bodies, such as doxapram and GAL021 (Galleon Pharmaceuticals Corp., USA). In this review we critically appraise the efficacy of these agents. We conclude that none of the experimental drugs are adequate for therapeutic use in opioid-induced respiratory depression and all need further study of efficacy and toxicity. All discussed drugs, however, do highlight potential mechanisms of action and possible templates for further study and development. **(Anesthesiology 2018; 128: 1027-37)**

IN contemporary medicine, the relief of moderate to severe pain is principally managed by treatment with opioid analgesic medication. Such drugs act at one or more of the opioid receptors within the central nervous system (CNS) and produce potent analgesia. However, these beneficial effects come with numerous side effects, including euphoria, nausea and vomiting, constipation, sedation, dizziness, respiratory depression, abuse, and addiction.[1] Opioid-induced respiratory depression occurs both in the acute and chronic treatment settings.[2–4] Although the occurrence of severe respiratory depression and related deaths in the treatment of acute and perioperative pain seems constant over the years (with an incidence of at least 0.5%),[1,5] over the last decade there has been a dramatic surge in fatalities from prescription opioids in chronic pain patients due to a dramatic increase in opioid consumption.[6–8] This is not surprising because opioids cause physical dependence and may trigger unsafe behavior such as abuse and misuse. The combination of dependence, abuse/misuse, and respiratory depression is potentially lethal. Opioid deaths in the community not only occur in patients but also in others due to selling, sharing, stealing, and diversion of prescribed tablets.[8]

Opioid-induced Respiratory Depression

Opioid-induced respiratory depression is caused by the activation of μ-opioid receptors expressed on the surface of neurons in brainstem respiratory centers.[1,9] For example, brain centers such as the pre-Bötzinger complex and the parabrachial nucleus are involved in respiratory pattern generation and express opioid receptors.[10,11] Activation of these opioid receptors by exogenous opioids may initiate respiratory compromise, which in many individuals is short-lived or reverts to normal breathing activity. In some individuals, often due to an opioid overdose or the combination of opioid use with other centrally depressant drugs (such as sleep medication or alcohol), diminished breathing progresses into irregular (or cyclic) breathing and eventually into apnea (the complete cessation of breathing). This may lead to cardiorespiratory collapse and ultimately death.[1–4,12] Currently, two main strategies emerge that are aimed at mitigation of opioid-induced respiratory depression and lowering the probability of opioid fatalities. One approach is the design of opioids with minimal respiratory effect (or at least a respiratory effect that is less than that

This is a 2017 Frontiers in Opioid Pharmacotherapy Symposium article.

Submitted for publication November 8, 2017. Accepted for publication February 20, 2018. From the Department of Anesthesiology, Leiden University Medical Center, Leiden, The Netherlands.

 Anesthesiology 2018; 128:1027–37

<zdoi;10.1097/ALN.0000000000002184>

observed with current available opioids); the other is the use of drugs that stimulate breathing through nonopioidergic pathways.[13] The discussion of novel opioids is beyond the scope of the current review and has been discussed in excellent reviews elsewhere.[14–23] Here, we focus on the discussion of respiratory stimulants that may be combined with opioid medication and then will prevent (rather than treat) opioid-induced respiratory depression without affecting analgesia.

Breathing is controlled by a complex brainstem neuronal network with inputs from higher brain centers and chemoreceptors located at central sites (*i.e.*, central chemoreceptors in the brainstem) and peripheral sites (*i.e.*, peripheral chemoreceptors in the carotid bodies situated at the bifurcation of the common carotid artery; fig. 1).[1,9] Various excitatory and inhibitory neuromodulators and receptors are involved in the generation of respiratory rhythm and tidal volume. Several mainly experimental drugs that interact with specific excitatory receptor systems within the respiratory network to offset opioid-induced respiratory depression are currently being studied. It is important to realize that because these stimulants should not interfere with analgesic efficacy or enhance opioid-related side effects (such as sedation and withdrawal), naloxone, a nonselective antagonist of the opioid receptors, seems not prudent in this respect because it rapidly reverses opioid-induced respiratory depression but at the expense of loss of pain relief or rapid induction of withdrawal.[1] Apart from its effect on analgesia, naloxone has additional disadvantages: it cannot reverse potent opioids with high affinity at the opioid receptor (*e.g.*, carfentanil, buprenorphine);[24] due to naloxone's short half-life, opioid-induced respiratory depression may reappear after some time (renarcotization);[1,25] and acute opioid withdrawal induces a surge in sympathetic activity, which may cause pulmonary edema, cardiac dysrhythmias, hypertension, and cardiac arrest in opioid tolerant individuals, as well as in opioid-naïve postoperative patients experiencing severe pain and stress.[1,26–30]

Most respiratory stimulants that we will discuss are still experimental, and we envision that such drugs will be given in the perioperative setting by continuous infusion or in the chronic setting as a separate pharmaceutical preparation (*e.g.*, tablet or patch) or combined in one formulation with the opioid. We will discuss and distinguish between drugs that act primarily at central (within the brainstem respiratory network) and drugs that act primarily at peripheral sites (at the carotid bodies). Certainly other agents than discussed below exist that theoretically could offset opioid-induced respiratory depression, such as the carbonic anhydrase inhibitor acetazolamide,[31] the antioxidants ascorbic acid and α-tocopherol,[32] the cholinesterase inhibitor physostigmine,[33] or the hormone progesterone.[34] All have been implicated as respiratory stimulants. However, their use in opioid-induced respiratory depression still warrants further research.

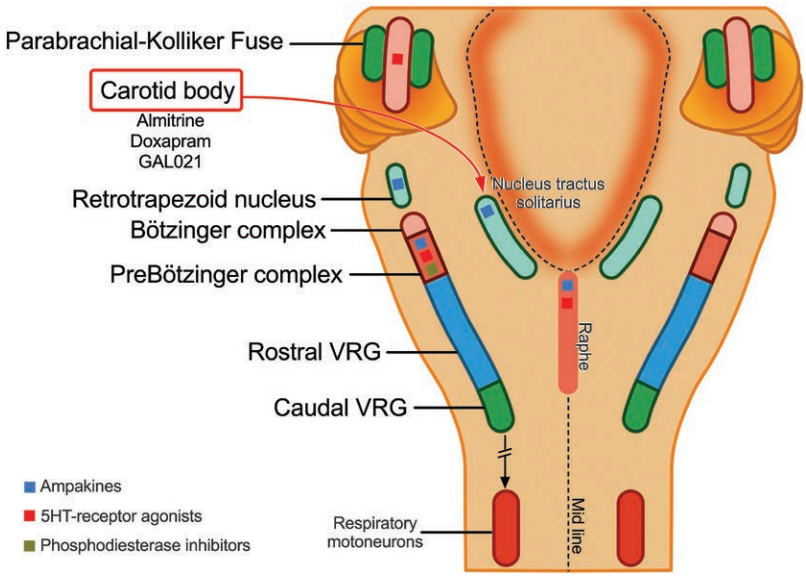

Fig. 1. Simplified schematic representation of the ventral aspect of the rat brainstem. The retrotrapezoid nucleus and midline raphe nuclei contain brainstem carbon dioxide-sensitive neurons (central chemoreceptors) that activate premotor neurons of the ventral respiratory group (VRG) that includes the pre-Bötzinger complex, an area with respiratory rhythm–generating neurons. Afferent sensory input from the peripheral chemoreceptors of the carotid bodies activates the nucleus tractus solitaries (*red arrow*), which also projects to the VRG. The VRG send signals to respiratory motoneurons in the spinal cord and phrenic nucleus that control intercostal muscles and the diaphragm. Another structure containing respiratory neurons is the pontine respiratory group (parabrachialis medialis and Kolliker–Fuse nucleus) that is implicated in volume and rate control. Other areas involved in ventilatory control (such as the locus coeruleus and areas in the cerebellum) are not depicted. The locations of action of ampakines, 5-hydroxytryptamine (5HT) agonists, and phosphodiesterase-4 inhibitors are indicated by *blue, red, and green colors,* respectively. Data redrawn from Dahan *et al*.[1] with permission.

Respiratory Stimulants Acting within the Brainstem Respiratory Network

We will discuss the following pharmaceutical agents with demonstrated efficacy in the reversal of opioid-induced respiratory depression by actions within the brainstem respiratory network: (1) α-amino-3-hydroxy-5-methyl-4-isoxazole-proprionic acid (AMPA) receptor agonists; (2) 5-hydroxytryptamine receptor agonists; (3) phospodiesterase-4 inhibitors; (4) D_1-dopamine receptor agonists; (5) glycyl-glutamine; and (6) thyrotropin-releasing hormone.

Ampakines

The AMPA receptor is an ionotropic transmembrane receptor for glutamate in the CNS. AMPA receptors are critically important for maintaining synaptic input, structure, and plasticity (see recent reviews).[35,36] AMPA receptors are present in key CNS centers of respiratory drive, such as the pre-Bötzinger complex, where they play an important role in the maintenance of respiratory rhythmogenesis and inspiratory drive, as well as sites outside the pre-Bötzinger complex (fig. 1).[37] Stimulation or inhibition of AMPA receptors, therefore, induces respiratory stimulant or inhibitory effects, respectively.[37,38] A wide variety of compounds may stimulate or modulate AMPA receptors and thus have a potential to act as respiratory stimulants in opioid-induced respiratory depression, but with AMPA receptors being located very widely throughout the brain, the introduction of site of action selectivity is of key importance. The complex structure of AMPA receptors, however, may help in this regard, there being a number of possible sites within the subunit structure of the AMPA receptor for drug interaction.[35] With regard to respiratory stimulation, the focus over recent years has fallen on to a family of benzamide compounds called ampakines,[13,37] which act allosterically to potentiate AMPA receptor–mediated synaptic responses.[39] Ampakines have been demonstrated to increase the respiratory drive in both animal and human studies, but only in hypoventilatory conditions. For instance, in a mouse model of Pompe's disease (a glycogen storage disease affecting muscle and nerve cells causing severe respiratory dysfunction), CX717 increased ventilation by increasing respiratory volume and frequency but not in wild-type mice.[40]

Hypoventilation induced by opioids is also reversed by amapkines in both animal and human models. In acute rat models, fentanyl-induced breathing depression was reversed by CX546 and CX717.[41,42] Importantly, CX717 is able to reverse or prevent deep levels of respiratory depression such as fentanyl-induced apneic events that without treatment would have been lethal.[42] Respiratory depression of inspiratory-related motoneuron activity induced by μ-opioid receptor agonist [D-Ala,[2] *N*-MePhe,[4] Gly-ol]-enkephalin in an *in vitro* preparation of rat hypoglossal nerve was reversed by CX614 and CX717.[43] Finally, in healthy human volunteers, alfentanil-induced respiratory depression was partly reversed by oral administration of CX717, but it led to an increase in tiredness during administration of the opioid.[44]

Given the results of both preclinical and experimental human studies, ampakines may represent a promising class of compounds for therapeutic use in opioid-induced respiratory depression without affecting opioid-induced analgesia.[45] CX1739 is a newer potent ampakine that reportedly readily crosses the blood–brain barrier, is metabolically stable, and has passed through phase I and II clinical trials in adults.[46] These researchers suggested a possible therapeutic use of this ampakine, that is, to treat apnea of prematurity in infants, because they showed that it improved respiratory drive in newborn rat pups that displayed slow breathing and marked apneas but was without effect if breathing of the newborn pups was faster with more stable rhythms and in older pups.[46]

Another drug that interacts with the AMPA receptor system is the antidepressant and cognitive enhancer tianeptine. Tianeptine induces neuroplasticity and modulates noradrenergic, dopaminergic, and glutamatergic pathways.[47,48] For example, tianeptine facilitates AMPA-mediated glutamatergic transmission and reduces AMPA receptor surface diffusion.[47,48] One animal study, which investigated the respiratory effects of tianeptine on morphine-induced respiratory depression, showed that tianeptine pretreatment prevented opioid-induced respiratory depression, similar to the effects observed after pretreatment with an ampakine (CX546) and without affecting antinociception.[49] Tianeptine is marketed currently in a number of countries primarily as an antidepressant, which could enable further clinical studies on this agent to be carried out to explore a possible therapeutic role to mitigate opioid-induced respiratory depression.

Although the number of animal studies is ample, there are very limited and insufficient human studies to support a possible therapeutic role of ampakines as respiratory stimulants in opioid-induced respiratory depression or other causes of hypoventilation, including a lack of safety and toxicity studies. Compounds that could possibly be suitable for human use include CX717 and CX1739 (and possibly tianeptine), especially with the observation in rats that deep levels of respiratory depression (including apnea) may be reversed or prevented by CX717.

Serotonin (5-Hydroxytryptamine) Receptor Agonists

Perhaps one of the most obvious targets for reversal of opioid-induced respiratory depression is to stimulate the respiratory system by activation of the 5-hydroxytryptamine system, because 5-hydroxytryptamine is a neuronal transmitter widely located throughout the respiratory control system.[9,50–52] For example, the pontomedullary system is an important central respiratory region comprising both inspiratory and expiratory functions. More specifically within the pontomedullary system, involved with respiratory rhythm generation and regulation, are the pre-Bötzinger complex and the Köllinker Fuse nuclei (fig. 1).[50–52] At these sites,

opioid and 5-hydroxytryptamine receptors influence respiratory functions but in opposite directions.[52] Hence, stimulation of opioid receptors, particularly μ-opioid receptors, induces depression of respiratory drive, whereas 5-hydroxytryptamine receptor stimulation enhances activity in respiratory neurons and reduces respiratory rhythm variability.[52–54] For example, the partial agonist buspirone has been shown to stimulate breathing (breathing frequency and minute ventilation) in the mouse at rest,[55] whereas the antagonist WAY100635 has been shown in mice to destabilize respiratory rhythm, possibly by an action at the Köllinker Fuse nuclei pontomedullary site.[56]

In various animal models, selective 5-hydroxytryptamine 1a receptor agonists reversed opioid-induced respiratory depression without compromising opioid-induced antinociception. For example, in rats, repinotan prevented morphine- and remifentanil-induced respiratory depression without compromising the antinociceptive effects of morphine and even prolonged those of remifentanil.[57,58] However, the effect of retinopan was dose-dependent with a reduced effect at higher doses (*i.e.*, bell-shaped dose-response curve). Some 5-hydroxytryptamine a1 receptor agonists not only reverse opioid-induced respiratory depression but also reduce opioid antinociception. One example is the selective 5-hydroxytryptamine 1a receptor agonist befiradol, which reversed fentanyl-induced respiratory depression (breathing rate and minute volume) in rats at the price of reduced fentanyl-induced antinociception.[59] Other 5-hydroxytryptamine receptors, including 5-hydroxytryptamine 4a receptors and 5-hydroxytryptamine 7 receptors, may be targets to reverse opioid-induced respiratory depression. For example, in rats, treatment with 5-hydroxytryptamine 4a receptor-specific agonist BIMU8 overcame fentanyl-induced respiratory depression and reestablished stable respiratory rhythm without loss of fentanyl analgesic effects[52]; in goats, the 5-hydroxytryptamine 4a receptor agonist zacopride reversed opioid-induced respiratory depression; and in rats, 5-hydroxytryptamine 1a/7 agonist 8-OH-DPAT reversed morphine-induced respiratory depression.[60,61]

5-Hydroxytryptamine 1a and 4a selective agonists have been investigated in humans for various clinical indications, although few studies have been carried out on the potential reversal of opioid-induced respiratory depression. The results of these limited studies, however, are negative. Neither clinical studies with buspirone nor with mosapride were able to demonstrate reversal of morphine-induced respiratory depression in healthy volunteers.[62,63] The negative results may be due to inadequate dosing and/or limited active site concentrations of drug being achieved due to limited CNS penetration of 5-hydroxytryptamine agonists.[64] This field is further hindered by the lack of drugs with high and specific selectivity for the various 5-hydroxytryptamine receptor subtypes, and all of the 5-hydroxytryptamine ligands discussed in this section have additional actions on other receptor sites. Buspirone, for example, is a partial agonist at 5-hydroxytryptamine 1a receptor but is also a dopamine autoreceptor antagonist and a dopamine D_3 receptor antagonist.[64] Further research is required to discover and investigate new agonists with greater selectivity, particularly at 5-hydroxytryptamine 1a receptor and related receptor sites.[65,66]

Phosphodiesterase-4 Inhibitors

Methylxanthine alkaloids such as caffeine, aminophylline, and theophylline stimulate respiratory rhythmogenesis and cause hyperexcitability of respiratory motor neurons by increasing cyclic adenosine monophosphate (cAMP) through inhibition of the enzyme phosphodiesterase 4 within the CNS.[67–69] Caffeine was used historically to treat opium and morphine poisoning and is still used to counter apnea of prematurity and stabilize breathing in preterm infants.[70,71] For example, a report from 1913 showed a brisk increase in respiratory rate after caffeine injection in rabbits pretreated with morphine.[71] Animal studies show that nonselective phospodiesterase-4 inhibitors caffeine and theophylline and the selective phospodiesterase-4 inhibitor rolipram reversed [D-Ala,[2] *N*-MePhe,[4] Gly-ol]-enkephalin–, fentanyl-, and morphine-induced depression of respiratory activity, without much effect on analgesic responses.[67–69] Furthermore, rolipram further improved incomplete recovery by theophylline of [D-Ala,[2] *N*-MePhe,[4] Gly-ol]-enkephalin–depressed respiratory activity.[68] Human data on the effect of methylxanthines on the relief of opioid-induced respiratory depression are sparse. A recent case report showed that 5 mg of caffeine was able to restore respiratory activity after remifentanil-induced apnea in a 65-yr-old patient.[72] Finally, in patients after propofol/remifentanil anesthesia, aminophylline shortened the time to return to spontaneous breathing, increased tidal volumes and respiratory rate, and increased bispectral index values compared to placebo.[73]

D_1-dopamine Receptor Agonists

D_1-dopamine receptor agonists activate cAMP–protein kinase A signaling within neurons of the respiratory network.[74–77] Down-regulation of cAMP–protein kinase A is an underlying cause of opioid-induced respiratory depression. In a series of animal experiments, it was shown that increasing neuronal cAMP after administration of potent opioids (fentanyl, [D-Ala,[2] *N*-MePhe,[4] Gly-ol]-enkephalin, enkephalin) restored breathing activity.[74–76] D_1-dopamine receptor agonists such as 6-chloro-APB and dihydrexidine increase cAMP levels *via* D_1-dopamine receptor-mediated stimulation of adenylyl cyclase.[74,75] Both 6-chloro-APB and dihydrexidine counter opioid-induced depression of respiratory rhythm, whereas dihydrexidine additionally restored fentanyl-induced impairment of ventilatory reactivity to carbon dioxide.[75] Both D_1-dopamine receptor agonists have no effect on fentanyl-induced antinociception. D_1-dopamine receptor agonists and cAMP, however, induce pharmacologic effects other than those on the respiratory system,

and selectivity of action must remain a question with this approach.

Glycyl-L-glutamine

Glycyl-glutamine (β-endorphin$_{30-31}$) is an endogenous dipeptide converted from the opioid peptide β-endorphine in proopiomelanocortin neurons in brain regions that regulate breathing and autonomic function (*e.g.*, nucleus of the tractus solitarius).[77–79] Glycyl-glutamine inhibits the firing frequency of brainstem neurons and has been shown to inhibit opioid-induced hypotension. Importantly, studies in the anesthetized and conscious rat show that glycyl-glutamine inhibits morphine-induced respiratory depression without affecting antinociception even at a high dose; glycyl-glutamine is without effect when respiration is not depressed by opioids.[79] More recently it was shown that glycyl-glutamine abolishes the rewarding effect of morphine by inhibition of morphine-induced dopamine release in the nucleus accumbens.[80] The receptor target of glycyl-glutamine remains still unknown, but the inability to antagonize its effects with opioid antagonists precludes an opioid receptor target.[77] Currently no human data are available on the effect of glycyl-glutamine on depressed breathing.

Thyrotropin-releasing Hormone

The tripeptide thyrotropin-releasing hormone (Glu-His-Pro-NH_2) is a potent but short-lived respiratory stimulant in animals and humans.[80–84] It induces rhythmic bursting in respiratory neurons of the nucleus tractus solitarius through modulation of membrane excitability.[81] In rabbit and monkey, thyrotropin-releasing hormone produces a rapid arousal from penthobarbital anesthesia.[85,86] Although in the rabbit single bolus infusions of thyrotropin-releasing hormone were unable to reverse morphine-induced respiratory depression,[85] studies in the vagotomized artificially ventilated rat showed that thyrotropin-releasing hormone and its analog RGH 22012 effectively antagonized morphine-induced respiratory depression as measured by diaphragmatic activity, possibly through an action at *N*-methyl-D-aspartate acid receptors.[87] Additionally, a more recent study showed that thyrotropin-releasing hormone antagonized morphine respiratory depression in an *in vitro* brainstem-spinal cord preparation from 1- to 4-day-old rats.[88]

Respiratory Stimulants Acting at the Carotid Bodies

Brainstem respiratory centers receive inputs from multiple sites to modulate breathing activity, most importantly from peripheral chemoreceptors at the carotid bodies located at the bifurcation of the common carotid artery.[89,90] Among other stimuli, the carotid bodies are particularly sensitive to changes in arterial P_{O_2}. Hypoxia causes a brisk hyperventilatory response, the mechanism of which has not been elucidated fully. One oxygen-sensing pathway involves K^+ channels expressed on so-called type 1 glomus cells, which are the oxygen-sensing cells of the carotid bodies.[89] Buckler and his research team[91–93] showed that hypoxia-induced depolarization of the carotid body was mediated through a K^+ channel of a type associated with the maintenance of background levels of potassium. This channel was different from the hitherto known conventional K^+ channels and was not blocked by conventional K^+ channel inhibitors, such as tetraethylammonium. The characteristics of these background, hypoxia- and acid-stimulated K^+ channels were identical to those of TASK-1 and TASK-3 channels.[91–93] TASK-1, TASK-3, and the heterodimer TASK-1/TASK-3 are tandem pore potassium channel subunits, with the latter heterodimer providing the predominant hypoxia-sensitive background potassium conductance in carotid body type 1 cells.[94] The K_{2P} potassium channel family (potassium channel subfamily K member 2; there are 15 members in humans) regulate background (or leak) potassium and determine membrane resting potential.

A number of K^+-channel blockers have been identified with respiratory stimulant properties that in fact mimic the effect of hypoxia at the carotid bodies. We discuss the following K^+-channel blockers with proven efficacy in reversal of opioid-induced respiratory depression: (1) almitrine, (2) doxapram, and (3) GAL021 (Galleon Pharmaceuticals Corp., USA; fig. 1).

Almitrine

Almitrine is a piperazine derivative that induces long-lasting stimulation of ventilation and increases the slope of the ventilatory response to carbon dioxide even under hyperoxic conditions (where peripheral ventilatory responses to carbon dioxide is greatly reduced).[95,96] None of these effects are observed after bilateral carotid body resection or after carotid sinus nerve denervation.[97,98] Further evidence for an effect of almitrine at the carotid bodies comes from feline studies using the dynamic end-tidal forcing technique by which central and peripheral components of ventilatory response to carbon dioxide are separated, and the stimulatory effects of almitrine were concluded to be entirely peripheral in origin.[99,100]

In dogs, almitrine was shown to antagonize the depressant effects of fentanyl on respiratory neurons recorded in anesthetized dogs.[101] Similarly, in patients after surgery, almitrine reversed fentanyl-induced respiratory depression without affecting analgesia.[102] However, almitrine does not represent a potential way forward in humans for treatment of opioid-induced respiratory depression because its marketing license was withdrawn by the European Medicines Agency in 2013 because of severe side effects, particularly peripheral neuropathy.[13,103,104] Almitrine was never licensed for use in Europe outside of France, Poland, and Portugal or in the United States.[13]

Doxapram

Doxapram (1-ethyl-4-[2-morpholinoethyl]-3,3-diphenyl-2-pyrrolidinone) is a respiratory stimulant acting at K_{2P} channels at type 1 glomus cells of the carotid bodies and

increasing tidal volume and respiratory rate.[105–107] It has been used clinically for more than 40 yr and is still licensed for use to stimulate respiration in a number of clinical conditions of compromised respiration[108] but not prescribed widely, possibly due to its analeptic side effect profile.

At low doses, doxapram has a respiratory stimulant effect exclusively at the carotid bodies, with loss of activity after bilateral sectioning of the carotid sinus nerves.[105,109,110] However, at higher doses of doxapram, nonselective, direct stimulation of medullary neurons is observed, and very early studies failed to show abolition of the action of doxapram by sectioning the sinus or vagus nerves in the dog.[110] More recently, studies in newborn rats support a greater role of a medullary action of doxapram on preinspiratory and inspiratory nerves in respiratory rhythm generation.[111] That doxapram exerts central actions is indisputable: doxapram shows marked CNS stimulant effects, but the relative contribution of the peripheral and central components to respiratory stimulation is less clear and seems dose-dependent.

Animal (mice, rats, rabbits) and human studies show that doxapram effectively reverses opioid-induced respiratory depression without compromising analgesia.[112–116] However, reversal of depressed ventilation is short-lived and ceases within 15 min after a single injection.[115] In humans, a single injection of doxapram administered during propofol/remifentanil anesthesia induced an increase in respiratory rate after 2 to 8 min but decreased significantly thereafter.[116] These observations are similar to the renarcotization seen after single doses of the μ-opioid receptor antagonist naloxone when used for recovery of respiration in opioid-induced respiratory depression.[1] In a recent study that illustrates the importance of understanding the pharmacokinetics and pharmacodynamics of both reversal agent and opioid, we studied the effect of a continuous infusion of doxapram on alfentanil-induced respiratory depression.[117] Doxapram reduced the plasma concentrations of the opioid, most probably related to a doxapram-induced increase in cardiac output. The reduced alfentanil plasma concentration was subsequently responsible for both a reduction in analgesia and a modest relief of respiratory depression. Finally, doxapram exhibits a considerable number of analeptic side effects (flushing, sweating, headache, nausea, hyperactivity, anxiety, panic attacks) that may limit its use.[13,108]

GAL021

A respiratory stimulant that is one of the latest claimants for a therapeutic use in opioid-induced respiratory depression is the experimental drug GAL021.[118,119] GAL021 (*N*-[4,6-*bis*-*n*-propylamino-(1,3,5)-triazin-2-yl]-*N*,*O*-dimethylhydroxylamine) is an analog of almitrine[13] but lacks a fluorinated piperazine ring of the type that may cause neuronal and muscular toxicity.[120] Like acute hypoxia, almitrine, and doxapram, GAL021 also acts as a K^+-channel blocker at the carotid bodies. Similar to almitrine, it acts through interactions with the large conductance Ca^{2+}/voltage activated K^+ channels. GAL021 predominantly stimulates breathing at the carotid bodies, because carotid sinus nerve transaction in the rat markedly diminished its hyperventilatory effect.[118] The respiratory stimulant properties of GAL021 have been demonstrated in healthy volunteers showing an increase in minute ventilation and a decrease in end-tidal carbon dioxide during a 1-h infusion.[118,119,121,122]

In animals (rat and monkey) intravenous GAL021 antagonized morphine-induced respiratory depression without affecting analgesia.[118] Also in healthy volunteers, continuous infusions of GAL021 reversed opioid-induced respiratory depression.[121,122] Integrated pharmacokinetic and pharmacodynamic analyses revealed that GAL021 showed a rapid attainment of maximal effect and a rapid onset time/offset time but with a reduced effect at deeper levels of respiratory depression (*i.e.*, ceiling effect).[122] Blood pressure and cardiac output during GAL021 infusion remain stable. These data indicate that GAL021 is a potential candidate for clinical use in opioid-induced respiratory depression and may demonstrate respiratory efficacy without comprising analgesia and with a favorable side-effect profile. Clearly, many further studies are still required to support the initial promise of this compound. For example, one final item that needs further study is the preliminary outcome from the pharmacokinetic-pharmacodynamic analysis that at deeper levels of opioid-induced respiratory depression GAL021 is less effective (ceiling effect).[121]

Discussion and Future Perspectives

We discussed seven pharmaceutical classes of nonopioid respiratory stimulants that could theoretically be used to prevent opioid-induced respiratory depression without compromising analgesia (table 1). Six of them act within the CNS (ampakines, 5-hydroxytryptamine agonists, phosphodiesterase-inhibitors, D_1-dopamine receptor agonists, the endogenous peptide glycyl-glutamine, and thyrotropin-releasing hormone), and one class acts at the carotid bodies (almitrine, doxapram, and GAL021; all are drugs that block background potassium channels of type 1 carotid body cells). Some are obsolete (almitrine), some seem more promising than others, but most of the drugs discussed are still experimental. It is our impression that none of them will be registered any time soon as respiratory stimulants because just a few studies with these compounds are currently being planned. We retrieved one (still nonrecruiting) study in the registry of the U.S. Library of Medicine (clinicaltrials.gov) on the effect of ampakine CX1739 in opioid-induced respiratory depression (identifier NCT02735629; website accessed January 3, 2018); no current or future studies on CX717 were retrieved. To the best of our knowledge, no further studies are being planned with GAL021 in compromised breathing (opioid-related or otherwise).

Although the drugs that we discussed are predominantly studied under acute conditions, the requirement in medicine for respiratory stimulants is much wider than just in the acute

Table 1. Overview of Animal and Human Studies on Nonopioid Reversal of Opioid-induced Respiratory Depression

	Animal Studies	Human Studies
Reversal of opioid-induced respiratory depression within the brainstem respiratory network		
Ampakines		
CX717	Respiratory stimulation in an animal model of Pompe's disease[40]; Reversal of fentanyl- and DAMGO-induced respiratory depression[42,43]	Reversal of alfentanil-induced respiratory depression[44]
CX546	Reversal of fentanyl- and morphine-induced respiratory depression[41,49]	
CX614	Reversal of DAMGO-induced respiratory depression[43]	
XD-8-17C	Reversal of TH030418-induced respiratory depression[45]	
Tianeptine	Prevention of morphine-induced respiratory depression[49]	
5HT agonists (receptor subtype)		
Buspirone (5HT1aR)		No effect on morphine-induced respiratory depression[62]
Repinotan (5HT1aR)	Prevention of remifentanil- and morphine-induced respiratory depression[57,58]	
Befiradol (5HT1aR)	Reversal of fentanyl-induced respiratory depression (but also of antinociception)[59]	
BIMU8 (5HT4aR)	Reversal of fentanyl-induced respiratory depression[52]	
Zacopride (5HT4aR)	Reversal of etorphine-induced respiratory depression[60]	
8-OH-DPAT (5HT1a/7R)	Reversal of etorphine- and fentanyl-induced respiratory depression[60,61]	
Mosapride (5HT4aR)		No effect on morphine-induced respiratory depression[63]
Phosphodiesterase-4 inhibitors		
Caffeine	Reversal of DAMGO- and morphine-induced respiratory depression[67,68]	Case report on reversal of remifentanil-induced respiratory depression[72]
Theophylline	Reversal of DAMGO-induced respiratory depression[68,69]	
Aminophylline		Shortening of time to spontaneous ventilation after propofol/remifentanil anesthesia[73,114]
Rolipram	Reversal of morphine-induced respiratory depression[67,68]	
D_1-dopamine receptor agonists		
6-Chloro-APB	Reversal of fentanyl-induced respiratory depression[75,76]	
Dihydrexidine	Reversal of fentanyl-induced respiratory depression[75,76]	
Glycyl-L-glutamine		
Glycyl-glutamine	Inhibits cardiorespiratory depression by β-endorphin and morphine[77–79]; Abolishes the rewarding effects of morphine[80]	
Thyrotopin-releasing hormone	No effect on morphine-induced respiratory depression in the rabbit[85]; Reversal of respiratory depression in *in vitro* and *in vivo* rat models of morphine-induced respiratory depression[86,87]	
Reversal of opioid-induced respiratory depression at the carotid bodies		
Almitrine	Reversal of fentanyl-induced respiratory depression[101]	Reversal of fentanyl-induced respiratory depression[102]; In humans associated with development of peripheral neuropathy
Doxapram	Reversal of fentanyl/droperidol- and morphine-induced respiratory depression[112,113,115]	Reversal of morphine- and alfentanil-induced respiratory depression[114,117]; Shortening of time to spontaneous ventilation after propofol/remifentanil anesthesia[116]
GAL021	Reversal of morphine-induced respiratory depression[118]	Reversal of alfentanil-induced respiratory depression[120,122]

DAMGO = [D-Ala,[2] *N*-MePhe,[4] Gly-ol]-enkephalin; 5HT = 5-hydroxytryptamine; R = receptor.

and perioperative setting. The number of patients that take opioids outside the hospital setting is soaring. For example, in The Netherlands opioid consumption has increased to 1.3 million users or 8% of the population in 2017, a more than 250% increase since 2004 (Dr. Dahan, unpublished observation, January 2018). Equally important is our experience that a large number of physicians that prescribe these drugs are not accustomed to dealing with the multifarious opioid side effects. In an increasingly aging population, more common obesity and a predisposition of such patients to obstructive sleep apnea and hence respiratory compromise, opioid treatment may easily produce life-threatening side effects. Additionally, opioid consumption for hedonistic pleasure, opioid use in opioid-naïve patients, or consumption together with centrally acting sedatives (including alcohol) will increase the risk of opioid-induced cardiorespiratory collapse. Finally and most importantly, the opioid epidemic has taken too many lives because of inadvertent overdose and fatal respiratory depression, and urgent measures are required. One such measure could be the further study and development of respiratory stimulants for prevention of opioid-induced respiratory depression.[123] For example, it might be of interest to study whether the combination of stimulants, for example combining a stimulant that acts at central sites and one that acts peripherally, increases the efficacy of respiratory stimulation under even deep levels of opioid-induced respiratory depression.

It is important to realize that life-threatening opioid-induced respiratory depression demands rapid and effective intervention. Such an action can currently only be achieved reliably by the administration of opioid antagonists such as naloxone. This is true in acute and chronic settings. So-called *take home naloxone* programs have been shown to reduce opioid overdose mortality rates, with little risks in naloxone administration by non–medically trained individuals.[124–126] Hence, nonopioid respiratory stimulants should be used as drugs that prevent rather than treat opioid-induced respiratory depression. Still, none of the available pharmaceutical agents highlighted in this review are currently adequately scrutinized to allow their therapeutic use in opioid-induced respiratory depression because they either have ample side effects that limit their use (*e.g.*, doxapram) or require further study of efficacy and toxicity. Nonetheless, these studies do usefully highlight potential mechanisms of action and possible templates for further study. In future experimental studies in human volunteers, we will further explore whether existing drugs such as tianeptine, ketamine, and thyroid-releasing hormone are viable alternatives to the experimental drugs discussed in this review.

Research Support

Support was provided solely from institutional and/or departmental sources.

Competing Interests

The Anesthesia and Pain Research Unit (Leiden University Medical Center, Leiden, The Netherlands) was or is involved in performing phase 1–2 studies on opioid-induced respiratory depression and its prevention funded by Center for Human Drug Research, Leiden, The Netherlands; Mundipharma Research Ltd., Cambridge, United Kingdom; Galleon Pharmaceuticals Corp., Horsham, Pennsylvania; and Grünenthal GmbH, Aachen, Germany.

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