overzichtsartikel

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Historical overview of (non-opioid) reversal agents of opioid-induced respiratory depression (OIRD)

Lessons from the past and new developments

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SAMENVATTING De ontwikkeling van geneesmiddelen waarmee opioïd-geïnduceerde ademhalingsdepressie (OIRD) kan worden voorkomen of behandeld blijft een grote uitdaging. Alhoewel er door de jaren aan een groot aantal stoffen een ademhaling stimulerend effect is toegeschreven, bleek het gebruik in de klinische praktijk beperkt door een smalle therapeutische breedte of door ernstige bijwerkingen. Sinds de introductie van naloxon is er een veilige behandeling voor OIRD. Naloxon antagoneert echter alle opioïdeffecten, waaronder ook het gewenste analgetische effect. Dit maakt naloxon weliswaar zeer nuttig voor de behandeling van levensbedreigende OIRD, maar het is ongeschikt als preventief middel. Recentelijk is aangetoond dat ampakines en kalium-kanaal blokkers zoals GAL021 ademdepressie door opioïden kunnen voorkomen zonder de analgetische werking te beïnvloeden en zonder ernstige bijwerkingen. In de komende jaren kunnen deze ademhalingsstimulantia een waardevolle aanvulling vormen op het arsenaal van de anesthesioloog.

ABSTRACT The development of respiratory stimulants and opioid antagonists to treat opioid induced respiratory depression remains one of the biggest challenges in respiratory research. A variety of substances with stimulatory effects on respiration have been shown to be of little use in clinical practice, either because of narrow margins of safety or due to serious side effects. With the introduction of naloxone a safe treatment for OIRD came within reach, although it reverses all opioid effects, thereby also affecting analgesia. This makes naloxone a very useful drug to treat life-threatening OIRD, but not efficacious for prevention of OIRD. Recent studies have shown that the development of ampakines and potassium-channel blockers such as GAL021 make prevention of OIRD without incidence of serious side effects possible. In the forthcoming years these respiratory stimulants might become a valuable addition to the anesthesiologists' armamentarium.

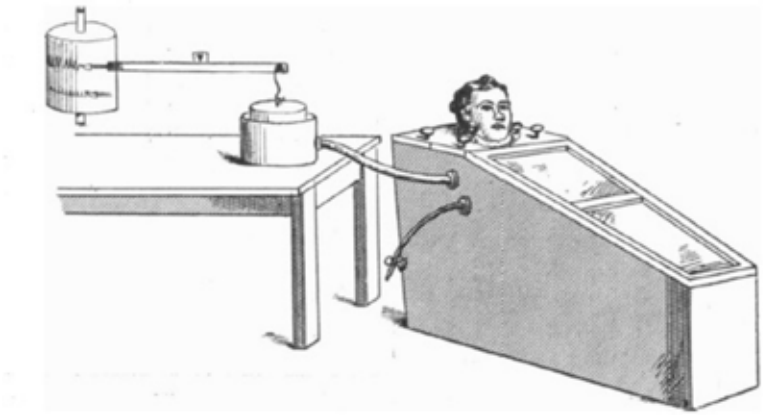

Figure 1. Body plethysmograph used by Haldane and Priestly (1905). All experimentations were performed on the authors themselves. Elevation of partial pCO2 was achieved by placing a sealed wooden box over the head. From Ref. 2.

Introduction

In humans, ventilation is driven by a complex physiological system that relies critically on intact peripheral and central chemosensors, a variety of interacting respiratory centers in the brainstem and higher brain centers. The system makes use of feedback and feed forward control aimed at maintaining rhythmic breathing and ensuring rapid adaptations to behavioral changes (such as eating, drinking, and exercising). In early years of anesthesia, with the introduction of chloroform and ether, respiratory depression was a major cause of morbidity and mortality, not only during surgery but also long after cessation of the procedure [1]. The high incidence of respiratory events prompted the pharmaceutical industry and anesthesia community to develop and use safer anesthetics, construct devices to protect and monitor ventilation and install measures that reduce the devastating sequels of severe respiratory depression (for example intubation and artificial ventilation). In modern anesthesia practice, respiratory depression, mainly opioid-induced respiratory depression (OIRD) remains an important issue, specifically when potent respiratory depressants are used under circumstances of reduced or minimal monitoring. One possible way to address or prevent respiratory depression from opioids or other agents is to administer respiratory stimulants that will reduce the probability of respiratory events without affecting the wanted end-points of drug treatment such as analgesia.

Until recently, research into respiratory stimulants was largely unsuccessful. Drugs that were developed either displayed severe adverse events, or the results in the preclinical setting could not be extrapolated to clinical practice. Moreover, respiratory stimulation is often a coincidental side effect of drugs developed for other indications. Current research that makes use of the recent insights in molecular pathways of the ventilatory control system led to the development of promising molecules that effectively reverse or prevent OIRD with minimal side effects. Examples are the ampakines (*e.g.* CX717) and potassium-channel blockers (*e.g.* GAL021). These new molecules possibly can reduce the occurrence of OIRD both in the perioperative setting as well as in chronic pain management with potent opioids.

Here we provide a short overview of respiratory stimulants that were used in the past and give a short impression of newly developed molecules.

The use of respiratory stimulants long time ago

Carbon Dioxide (CO_2)

The first experiments with CO_2 on human subjects were performed by Haldane and Priestly in the beginning of the 20th century in Oxford (see Figure 1) [2]. These experiments evaluated the effects of varying alveolar concentrations of CO_2 at different atmospheric pressures, fluctuating concentrations of oxygen and various levels of physical exercise to test their – at that time novel – hypothesis that CO_2 partial pressure (pCO_2) in the respiratory center was the main driving force of ventilation. This hypothesis was based on earlier work by Haldane and Lorrain Smith in the 19th century; they studied possible reasons for the high death rates in overcrowded dwellings [3]. They concluded that the increase in ventilation caused by the increase in the level of CO_2 was similar to the tachypnea during physical exercise, while the increase in ventilation caused by depletion of oxygen was distinctly different, since hypoxia produced subjective sensations of cyanosis [3].

By identifying alveolar pCO_2 as the most important factor driving respiration and affirming that changes in pCO_2 were transferred to the respiratory center through arterial blood instead of *via* vagal or sympathetic stimulation of the respiratory center, Haldane and Priestly dramatically changed the way respiratory regulation was perceived. They concluded that the respiratory center attunes to changes in arterial PCO_2 ($PaCO_2$). Elevating $PaCO_2$ increases ventilation drastically, whereas decreases in $PaCO_2$ will eventually lead to apnea [2]. Although a potent stimulant, CO_2 has been of little practical use by itself to treat opioid induced respiratory depression. It has been used to coerce the anesthetized patients into hyperventilation in order to rapidly exhale inhaled anesthetics [4]. But the practice of pouring 100% CO_2 over the face, for several breaths, did not become common practice. Reservations to use CO_2 as a respiratory stimulant were caused by the notion that an increase in $PaCO_2$ would cause depression of the central nervous system. This idea originated from research in the early 19th century when Hickman first successfully induced CO_2 narcosis in animals (an experiment designed to prove that CO_2 may be used in

humans for anesthesia as well) [6]. Further research on acute exposure to CO_2 showed that exposure to 10.4 % CO_2 produced a profound increase in ventilation approaching maximal voluntary ventilation, as well as a decreased level of consciousness in some subjects [7]. A case-report of a patient with muscular dystrophy suffering from respiratory failure and an altered state of consciousness attracted much attention [8]. The $PaCO_2$ measured in this patient was approximately 8 kPa, which became the upper limit above which CO_2 narcosis would likely occur. Recent, unpublished data from our laboratory show that CO_2 exposure of 9 and 10% (up to 1 h) in healthy male volunteers causes attentional narrowing and agitation apart from extensive respiratory stimulation; CO_2 induced narcosis was not observed [9].

Atropine

Atropine is a substance long thought to have a stimulatory effect on respiration. Data regarding such an effect however are at best ambiguous. A first study published in 1914 found that atropine produced an increase in minute volume of approximately 15% [10]. However, in a later study evaluating the effect of 16.3 mg morphine and 1.3 mg atropine, little change in respiratory rate was observed [11]. In yet another study, the exact same combination did produce an effect on pulse rate and a slight recovery of OIRD [12]. This is evidently somewhat surprising taken the high dose of morphine used in this study. Finally, in the first "randomized controlled trial" (dated 1957) evaluating the effect of atropine on the ventilatory response to inhaled CO_2 (hypercapnic ventilatory response or HCVR), no beneficial effect was observed on opioid-induced respiratory depression [23].

Caffeine

Caffeine, a methylxanthine alkaloid, was used historically to treat opium and morphine poisoning. Initially promising studies in rabbits showed a brisk increase in respiratory rate immediately following intravenous injection of caffeine to animals that were pretreated with morphine (See Figure 2) [14]. The first study that systematically evaluated the effect of caffeine in humans did not show an increase in respiratory rate, but did show a significant increase in alveolar ventilation and elimination of carbon dioxide (note that this was based on two subjects only) [10]. Subsequent studies could find some respiratory stimulation from caffeine but the effects were modest. For example, in a study comparing the effects of several stimulants on morphine-induced respiratory depression, caffeine produced just 17% increase in ventilation (whereas amphetamine more than doubled ventilation) [15]. The American anesthesiologist Jay Bellville studied the effect of 250 mg caffeine (the equivalent of five cups of coffee) on top of opioid depressed breathing in the early 1960s at Stanford University [16,17]. Only a clinically insignificant ventilatory effect was observed. Although caffeine is no longer considered capable of reversing OIRD, it has proven to be a useful treatment option in neonatology, e.g. in premature neonates with low birth weight. Caffeine reduces the incidence of bronchopulmonary dysplasia, facilitates earlier discontinuation from the ventilator and improves the rate of survival with reduced neurodevelopmental disability at 18 to 21 months in infants with low birth weight [18-21]. The mechanism underlying the association of this favorable outcome and the use of caffeine is still unclear. Recent animal data show that caffeine possibly affects brainstem respiratory rhythmogenesis or causes hyperexcitability of motor networks involved in respiration by inhibiting phosphodiesterase [22, 23]. Interestingly the difference in efficacy of caffeine between neonates and adults could be related to maturational changes in chemosensory responses [24].

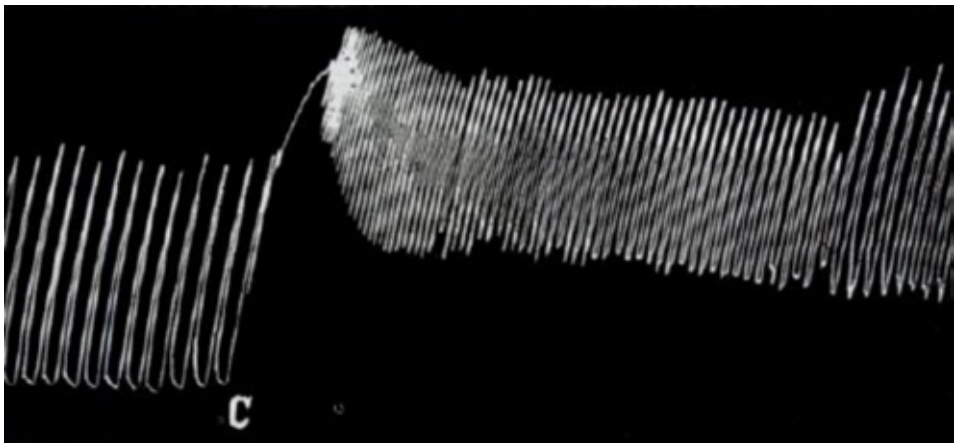

Figure 2. Respiratory tracing in the rabbit. An intravenous injection of 10 mg caffeine given at C causes an increase in respiratory rate at the background of morphine-induced respiratory depression. From Ref. 14.

Naloxone

In 1915 the German pharmacologist Julius Pohl discovered n-allyl-norcodeine and observed that – although inactive when administered alone – it antagonized respiratory depression caused by morphine [25]. The value of this discovery was not recognized until the early 1940s when (based on the finding of Pohl) N-allyl-normorphine or nalorphine was developed, a morphine derivative [26-29]. This became the first agent to be widely applied as reversal agent of severe OIRD by restoring respiratory rate and tidal volume. Nalorphine was not only used to treat opioid overdose but also for the identification of a hidden opioid addiction [30]. Efforts to find an ideal morphine and nalorphine dose combination to produce analgesia with minimal effects on respiration, led to the discovery that nalorphine also holds analgesic properties due to its opioid agonist-antagonist properties. Unfortunately nalorphine causes dysphoric and psychomimetic side-effects limiting its routine clinical use [31].
A suitable alternative was found in naloxone, an alkyl-derivative of noroxymorphone, first synthesized in 1960 (see Figure 3). It is up to thirty times more effective in antagonizing OIRD than is nalorphine [32]. Naloxone is a non-selective competitive opioid antagonist at μ-, δ-, and κ-opioid receptors and reverses all pharmacological effects of opioids (including analgesia, sedation, respiratory depression) in a dose-dependent fashion

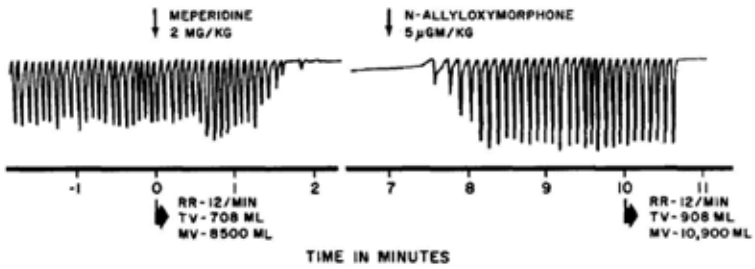

Figure 3. First in man study displaying reversal of meperidine induced OIRD by naloxone. From Ref. 33.

[33]. Naloxone is a lipophilic molecule and consequently rapidly passes the blood-brain-barrier with a near immediate effect following intravenous administration. The elimination half-life of naloxone is about 33 minutes [34]. For opioids with an elimination half-life >33 minutes (morphine, methadone) there is always the risk of re-narcotization and one should consider a continuous naloxone infusion to treat severe intoxications. Naloxone is currently the treatment of choice for OIRD. The amount of naloxone necessary to reverse respiratory depression depends on the opioid that requires antagonism (opioids differ in their affinity for the μ-opioid receptor and consequently in the ability of naloxone to disperse the opioid from the receptor) and the opioid dose [35]. In the perioperative setting, titration to effect is common practice using 40 μg bolus infusions.

Aminophylline

The respiratory effects of aminophylline, a methylxanthine alike caffeine, are known since the 1960s, predominantly in the treatment of asthma. Aminophylline causes the translocation of calcium, inhibition of phosphodiesterase and blockade of the adenosine receptor [36]. These mechanisms are thought to contribute to the effects of aminophylline: bronchial muscle relaxation, improvement of diaphragm contractility, increase in the activity of the inspiratory muscles, augmentation of the hypoxic ventilatory response and decrease of the incidence of postoperative apnea in preterm neonates [37-39]. Recently, the effect of 3 mg/kg aminophylline (3 mg/kg) in propofol/remifentanil anesthesia was studied in adults. Aminophylline shortened the time to return of spontaneous breathing, increased tidal volumes and respiratory rate and increased BIS values compared to placebo [40]. However, aminophylline was also associated with a significant increase in heart rate, as already described earlier [41].

Doxapram

Despite their respiratory effects, analeptics are hardly ever used as respiratory stimulants, mainly because of their severe side effects (convulsion, hypertension) [42]. Newer synthetic analeptics, such as doxapram, were designed to specifically stimulate respiration without causing unwanted side effects [43-45]. In two studies in postoperative patients (performed in the mid-1960s), doxapram caused a moderate to intense increase in minute volume that peaked within 2.5 min but dissipated within 5 min [43, 44]. The most important mechanism of action of doxapram is inhibition of K^+-channels expressed on the membrane of peripheral chemoreceptors cells of the carotid bodies [46]. This leads to the local release of neurotransmitters (*e.g.* ATP, acetylcholine) that stimulate nerve endings of the sinus nerve, much alike the effect of hypoxia on the carotid bodies. The end-point of the K^+-channel inhibition is a brisk hyperventilatory response. Recently, it was shown 1 mg/kg doxapram decreased the recovery period in perioperative patients after propofol/remifentanil anesthesia by optimizing (increasing) spontaneous breathing [40]. We recently studied the influence of doxapram on alfentanil-induced respiratory depression (arterial plasma concentrations 60-100 ng/ml). Doxapram (total dose of 2.7 mg/kg administered over 90 min) had no effect on ventilation [47]. However, doxapram had robust sympathicoexcitatory effects with an increase in cardiac output and heavy perspiration, which limited a further increase in dosing. We attribute the differences in study outcomes to the evident differences in study methodology and setting (such as the differences in the opioid administration). Although doxapram is nowadays hardly ever used in adults, in preterm infants it is used to prevent apnea [48, 49]. Negative effects on cerebral oxygenation and long-term mental developments limit its use [48]. Still, doxapram has recently been reintroduced in preterm infants not responsive to methylxanthines. In a five year evaluation of the use of respiratory stimulants in two neonatal centers in the Netherlands, 8% of premature infants < 32 weeks gestational age, were treated with doxapram [49]. In 2004, a Cochrane review of doxapram treatment for apnea in preterm infants concluded that intravenous doxapram reduces apnea of prematurity and its success rate is comparable to methylxanthines [50]. A recent study found that doxapram [0.2 mg/kg/h, max 1.0 mg/kg/h] combined with methylxanthines, produced similar results compared to methylxanthines alone, showing an 80% reduction in apnea frequency with minimal side effects [51].

Almitrine

Almitrine was developed in the 1970s. It can be administered intravenously and could be used perioperatively as a respiratory stimulant. Almitrine increases tidal volume and respiratory rate, especially under conditions of hypercapnia and hypoxia [52, 53]. Alike doxapram, almitrine stimulates afferent carotid body nerves mimicking hypoxic stimulation of the peripheral chemoreceptors [54]. In addition to the effect exerted at the carotid bodies, almitrine improves the ventilation-perfusion ratio and increase oxygenation in patients diagnosed with chronic obstructive pulmonary disease [55]. However, almitrine is considered unsuitable for clinical practice due to the peripheral neuropathy caused by it's metabolites [52, 56].

Ampakines

Ampakines are drugs that modulate the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors. AMPA receptors are involved

in glutamatergic transmission and are essential for maintaining respiratory rhythmogenesis in the brainstem.
In a first study in humans, the ampakine CX717 was tested on alfentanil-induced respiratory depression [57]. CX717 increased respiratory frequency, hemoglobin oxygenation and VE_{55} (minute volume at a fixed end-tidal pCO_2 of 55 mmHg). Pain tolerance to heat and electrical stimuli did not differ between groups. However, subjects on CX717 reported increased sedation. Another interesting finding was that CX717 might be efficacious in maintaining airway patency. Opioids do not only depress rhythmogenesis, but also depress hypoglossal nerve activity causing a decreased airway patency [58]. Cell patch recordings from hypoglossal motoneurons treated with the opioid DAMGO show that CX717 counteracts the inhibitory opioid effect, however the exact mechanism remains unknown [59]. This suggests that CX717 might be a promising drug in the treatment/prevention of upper airway obstruction in patients with sleep-disordered breathing.

GAL021

The latest addition and possibly most promising respiratory stimulant is GAL021 (a derivative of almitrine, however without harmful metabolites). It inhibits calcium-activated potassium (BKCa) channels, thereby mimicking the effect of acute hypoxia at the carotid bodies. In the first in-man trial, GAL021 increased ventilation without causing any serious side effects [60]. We determined in our laboratory the effect of GAL021 on alfentanil-induced respiratory depression in healthy volunteers. During GAL021 infusion, respiratory rate and tidal volume increased significantly compared to placebo infusion, whilst analgesia and sedation were not affected by the drug [61]. The pharmacokinetic-pharmacodynamic (PKPD) analysis of the data determined that GAL021 has a rapid onset of action and a very profound capability to reverse OIRD. However, the effect of GAL021 is less pronounced in severe opioid-induced respiratory depression, and higher dosages of GAL021 then only have a limited effect. These human data indicate that GAL021 is an excellent drug for the adjuvant administration with opioids used for the treatment of chronic pain [62].

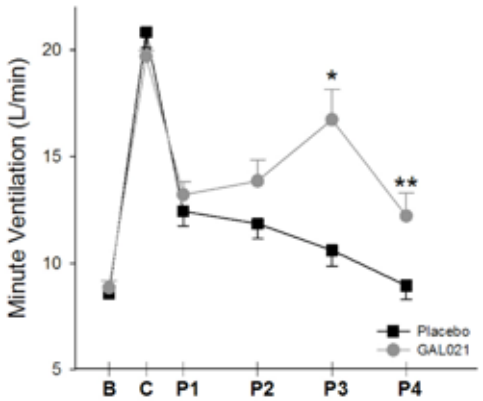

Figure 4. Effect of GAL021 on opioid induced respiratory depression B: baseline (no drug, no added inspired carbon dioxide), C: the carbon dioxide clamp before any drug infusion, P1: low-dose alfentanil (ALF) infusion before any GAL021 or placebo infusion (carbon dioxide-clamp plus ALF-low), P2: the combination of low-dose alfentanil and low-dose GAL021 or placebo (carbon dioxide-clamp plus ALF-low plus GAL021-low), P3: the combination of low-dose alfentanil with high-dose GAL021 or placebo (carbon dioxide-clamp plus ALF-low plus GAL021-high), and P4: the combination of high-dose alfentanil with high-dose GAL021 or placebo (carbon dioxide-clamp plus ALF-high plus GAL021-high). Values are mean ± 95% CI. *P ← 0.01 versus placebo. From Ref. 61.

Conclusions

Prevention of opioid induced respiratory depression has been a spearhead in the area of respiratory research in anesthesia. Over the years, an array of compounds have been examined, but rendered useless either due to clinically irrelevant effects or due to the presence of serious side effects. Currently, ampakines and the BKCa-channel blocker GAL021 are the most promising respiratory stimulants that probably may be used in the near future to prevent opioid induced respiratory depression.

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