Incidence, Reversal, and Prevention of Opioid-induced Respiratory Depression

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ABSTRACT

Opioid treatment of pain is generally safe with 0.5% or less events from respiratory depression. However, fatalities are regularly reported. The only treatment currently available to reverse opioid respiratory depression is by naloxone infusion. The efficacy of naloxone depends on its own pharmacological characteristics and on those (including receptor kinetics) of the opioid that needs reversal. Short elimination of naloxone and biophase equilibration half-lives and rapid receptor kinetics complicates reversal of high-affinity opioids. An opioid with high receptor affinity will require greater naloxone concentrations and/or a continuous infusion before reversal sets in compared with an opioid with lower receptor affinity. The clinical approach to severe opioid-induced respiratory depression is to titrate naloxone to effect and continue treatment by continuous infusion until chances for renarcotization have diminished. New approaches to prevent opioid respiratory depression without affecting analgesia have led to the experimental application of serotinine agonists, amapkines, and the antibiotic minocycline.

OPIOID analgesics remain the most commonly used drugs in the treatment of moderate to severe postoperative pain. The opioids that have been used for decades (such as morphine, methadone, and fentanyl) have become accepted treatments and are administered to patients by anesthesiologists under standard protocols. Side effects related to opioid use have become well known and may be managed appropriately, with nausea, vomiting, sedation, and respiratory depression being associated commonly with postoperative analgesic doses. However, these side effects should not be trivialized. Postoperative nausea and vomiting is common and distressing to patients, and excessive sedation may contribute to increased morbidity and mortality.1 However, it is perhaps respiratory depression that remains the main hazard of opioid use, uppermost in the minds of nurses and physicians, because of the obvious risk of fatal outcome. The first recorded human fatality from a morphine overdose dates from the 1850s.3 The Englishman Alexander Wood (1817–1884) performed one of the first injections of morphine to his wife who subsequently died from respiratory depression. The toxic effects of morphine were noted earlier by Sertürner, the German pharmacist who was the first to isolate morphine from opium in 1806. In 1817, he published his discovery together with reports of the administration of the alkaloid to himself, three young boys, three dogs, and a mouse. One of the dogs died while he described the effect that morphine had on himself and his three young “volunteers” as near fatal.5

Since the recognition in the 1960s that opioid ligands exert their biologic effects in vivo through interactions with multiple opioid receptors, namely μ-, δ-, and κ-opioid receptors,6 it has been recognized that opioid-induced respiratory depression is mediated largely by the μ-opioid receptor(s). This has been substantiated more recently using the technique of knockout mice lacking selective receptor gene products. In knockout mice lacking μ-opioid receptors, in contrast to mice with active μ-opioid receptors, administration of morphine and other opioids failed to induce respiratory depression (or centrally mediated antinociception).7 Therefore, the evidence that respiratory depression and antinociception seem to act in tan-
and/or oxygen saturation (SpO₂). For example, in a series of studies in the 1990s, Wheatley and coworkers 12–15 used SpO₂ as a measure of respiratory effect and defined postoperative hypoxemia as SpO₂ < 94% with moderate hypoxemia as SpO₂ < 90% and severe hypoxemia as SpO₂ < 85% for more than 6 min per hour. Definitions of what levels may constitute respiratory depression, however, will vary between practices or studies (e.g., Catley et al.16 who used SpO₂ level of < 80%). With respect to breathing frequency, severe respiratory depression is considered at breathing rates of less than 8–10 breaths/min. It is important to understand that oxygen saturation and breathing frequency are surrogate indicators of ventilatory drive and provide only limited information on the effects of a drug on the ventilatory control system (e.g., oxygen saturation is a measure of gas exchange in the lung rather than a direct indicator of ventilatory efficacy).17 Inspired minute ventilation and arterial carbon dioxide concentration in clinical settings and the hypercapnic ventilatory response in experimental settings are direct measures of ventilation and ventilatory drive but are often difficult to assess on a continuous basis. However, SpO₂ is a simple measurement used commonly to indicate a serious opioid-induced ventilatory event, perhaps together with even looser indicators of respiratory depression such as sedation and bradypnea (i.e., low breathing frequency).

There have been various studies comparing different routes of administration of opiates, particularly morphine, on respiratory depression in postoperative care. In a meta-analysis of intramuscular, epidural, and intravenous analgesia (including patient-controlled analgesia [PCA]), the incidence of opioid-induced respiratory depression as defined by low-breathing frequency was less than 1%.18,19 Most of the studies included were designed to compare analgesic effects, but respiratory effects, if any, were usually reported as side effects. Data from a large meta-analysis including 15 clinical trials (comparing intramuscular morphine (10 mg) in 486 patients with placebo in 460 patients) indicate that the occurrence of minor adverse effects were more common with morphine (34%) than with placebo (23%), but major adverse events were rare and did not differ between morphine and placebo (morphine 0.6% and placebo 2%).19 Absence, or very low incidence, of respiratory depression with single or repeated doses of intramuscular morphine (10 mg) is a common finding of postoperative studies, exemplified by a very recent study in which a 10-mg dose of morphine was compared on intramuscular and intravenous administration to 38 patients with postoperative pain after hip replacement surgery.20 Neither treatment caused severe respiratory depression. Epidural and intrathecal administration of opioids was shown in the 1980s and 1990s to provide effective and long-lasting postoperative analgesia, and the use of low-dose opioids was advocated.21,22 In two large reviews of more than 14,000 and 11,000 patients receiving opioids extradurally, with the majority being administered morphine for the treatment of postoperative, traumatic, and cancer pain, the incidence of severe respiratory depression was 0.09% and 0.2%, respectiv
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Reversal of Opioid Effect

Naloxone Reversal of Opioid-induced Respiratory Depression

Reversal of Full Opioid Agonists (Morphine, Fentanyl, and Congeners)

Two opioid antagonists are available clinically as rescue medications for serious opioid-induced side effects: naloxone and naltrexone. Naloxone is United States Food and Drug Administration approved for therapeutic use in the reversal of opioid-induced activity and adverse reactions postoperatively, including respiratory depression. Naltrexone is approved for use in alcoholism and opioid dependence. Clinically, naloxone has been shown in many studies to reverse effectively and rapidly respiratory depression induced by opioid full agonists, such as morphine and fentanyl.

Naloxone is an allyl-derivative of noroxymorphone and first synthesized in 1960 (fig. 2). It is a nonselective competitive opioid antagonist at the μ, δ, and κ-opioid receptors. Naloxone inhibits all pharmacological effects of opioids and, in line with classic receptor theory, produces a parallel right shift in the dose-response curves of opioids. Naloxone is readily absorbed after oral administration, but its low bioavailability makes naloxone less suitable for this administration route. After oral administration, naloxone is metabolized extensively in the liver (first-pass effect > 95%). It is primarily metabolized into the inactive conjugate naloxone-3-glucuronide. After intravenous infusion, approximately 70% is excreted through the kidney as conjugated naloxone metabolites and 30% as unchanged naloxone.

The extent and duration of naloxone-induced reversal of opioid-induced respiratory effects is highly variable and related to many factors, including the specific opioid used, the opioid dose, administration mode, concurrent medication,
underlying disease, pain and the state of arousal, genetic
make-up of the patient, and exogenous stimulatory factors.
It is, therefore, important to understand the pharmacokinet-
ics and pharmacodynamics of the specific opioid agonist,
antagonist, and their interactions for effective and safe rever-
sal of opioid-induced respiratory depression.

For naloxone, the relationship between dose of agonist
and antagonist for respiratory depression has been dem-
onstrated quantitatively in mice. Apparent pA2 values (log of
the affinity constant KB) were determined for the antago-
nism by naloxone of the respiratory depressant effects of
three opioid agonists: morphine, levorphanol, and pentazo-
cine; the apparent pA2 values were not significantly different
for the three opioids (apparent pA2 = 7.35, 7.49, and 7.46,
respectively), indicating that all three drugs most probably
interact with the same receptor (i.e., the µ-opioid receptor)
to induce respiratory depression. To obtain these pA2 val-
ues, as a competitive antagonist at the µ-opioid-receptor
complex, the activity dose response curves to opioid agonists
are shifted in parallel to the right in the presence of naloxone.

Hence, the higher the dose of opioid agonist administered,
the greater the dose of naloxone needed to reverse the opioid
effects (particularly of the respiratory depressant effects ob-
erved with the higher agonist doses). The receptor associa-
tion or dissociation kinetics (fig. 1) for naloxone are fast. In
vitro, the half-life of dissociation (t1/2k0) of the naloxone-
opioid human µ-opioid-receptor complex has been esti-
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see the next section Reversal of the Partial Opioid Receptor Agonist Buprenorphine). Often cumulative naloxone titration doses much less than 400 µg are then sufficient. Note that respiratory depression occurs at higher receptor occupancy than some degree of analgesia, and hence, analgesia is not compromised when titrating naloxone to (respiratory) effect. However, this evidently does not apply to the setting of drug abuse or suicide attempt. It also does not apply to shorter acting opioids, such as alfentanil, when continuous zero-order infusion regimes are applied. Such an approach may have benefits in minimizing the fluctuations in drug plasma levels, but agonist infusions have obvious implications for the time scale for the reversal by naloxone. In two studies in healthy volunteers, the respiratory depressant effects of a continuous infusion of alfentanil were reversed rapidly and completely by a single bolus infusion of naloxone (approximately 0.4 mg).47-48 However, if the alfentanil infusion is maintained, the depressant effects of alfentanil were reasserted within the hour.48 Possibly, improved infusion regimens such as by using target-controlled infusion may reduce the chance of respiratory depression without compromising analgesia.

One strategy that has been investigated to prevent the recurring return of opioid adverse events is the use of continuous or repetitive naloxone infusion. In small-scale studies, fixed-dose infusions of naloxone of approximately 4–8 µg · kg⁻¹ · h⁻¹ were used to maintain postoperative patients breathing effectively after having received morphine, sufentanil, or fentanyl.49 This strategy has been expanded more recently to investigate whether infusions of naloxone could be titrated in an up-and-down manner to maintain adequate spontaneous respiration after high-dose fentanyl anesthesia.50 Patients (n = 59) scheduled for elective surgery for visceral cancer received an infusion of fentanyl (40 µg/kg for more than 30 min before incision followed by a basal infusion of 4 µg · kg⁻¹ · h⁻¹) and, after surgery, extubation was assisted and maintained by the administration of naloxone. Naloxone boluses were administered as required to achieve set extubation criteria, followed by an up-and-down program of naloxone infusions to maintain adequate analgesia combined with adequate breathing. The mean total doses of naloxone were for extubation 3.4 ± 2.6 µg/kg and for maintenance 26.9 ± 23.2 (mean ± SD) µg/kg over a mean 10.8 ± 6.7 h (mean 2.4 µg · kg⁻¹ · h⁻¹). In the postoperative period, manipulating the naloxone infusion rates as required successfully resolved any symptoms observed. It should be noted perhaps that one patient was excluded from the postoperative part of the study because of failure to establish adequate spontaneous respiration with the maximal dose of naloxone for extubation (600 µg).

A different strategy has been advocated for remifentanil, a µ-agonist agonist with a similar analgesic potency to fentanyl, but a very fast onset (τ₁/₂α = 1 min) and an ultra-short duration of action caused by rapid hydrolysis to an inactive metabolite (plasma elimination τβ = 3 min).46-51 In healthy volunteers, remifentanil-induced respiratory depression and its reversal by naloxone have been investigated. Twelve subjects received remifentanil as low-dose (0.025 µg · kg⁻¹ · min⁻¹) or high-dose (0.1 µg · kg⁻¹ · min⁻¹) infusions, and all subjects showed significant reductions of the respiratory hypoxic drive, observable 10 min after infusion commencement and for the duration of the infusions.58 A bolus dose of naloxone (0.6 µg/kg) was administered after 95 min of the continuous remifentanil infusion. There was no reversal effect of naloxone on the high dose and only a modest effect on the low dose of remifentanil. The two possible explanations of this lack of reversibility of remifentanil by naloxone discussed are (1) even the low-dose infusion maintained a concentration of remifentanil at the receptor level that the (fixed) dose of naloxone was unable to displace or (2) the thermodynamics of the remifentanil—receptor interaction is such that competitive antagonism is difficult to demonstrate.48 In comparison, for remifentanil with its ultra-short half-life, simply stopping the infusion was a very effective way of reversing the respiratory actions; a reversal complete within approximately 10 min of infusion termination, an effect just as rapid as the naloxone-induced reversal of alfentanil-induced effects. Hence, for remifentanil, reversal of adverse events is preferable by termination of infusion, rather than administration of naloxone. If naloxone is used for reversal, however, higher than standard doses may be required or a continuous infusion needs to be applied.

Notably, in a recent study comparing remifentanil and fentanyl for postoperative pain control after abdominal hysterectomy, the patient group receiving remifentanil infusions (0.05 µg · kg⁻¹ · min⁻¹ over 2 days) was associated with 3 episodes of serious respiratory depression (3 of 28 patients, 10.7%), and the study was closed.55 No events of serious respiratory depression were observed in the fentanyl group (0.5 µg · kg⁻¹ · min⁻¹). Respiratory depression and apnea, therefore, may be of particular concern with remifentanil infusion. Respiratory complications with remifentanil may further be associated with its rapid onset where the carbon dioxide ventilation response curve (the relationship between minute volume and arterial carbon dioxide concentration) is altered before the patient’s arterial carbon dioxide concentration rises sufficiently to sustain ventilatory drive.17,53,54

Reversal of the Partial Opioid Receptor Agonist Buprenorphine

A commonly used long-lasting, partial opioid agonist that has a complex interaction with naloxone is buprenorphine. Some early clinical studies indicated that, typical of opioids, buprenorphine could induce respiratory depression, but that this effect was resistant to antagonism by naloxone requiring higher than usual doses for even a partial reversal.53-57 In a study in human volunteers, neither the level of sedation nor respiratory depression induced by buprenorphine (0.3 mg/70 kg) was consistently reversed by naloxone, even with high doses (10 mg).58

Buprenorphine has a half-life in plasma of approximately 3 h, although its duration of action is considerably longer

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tions with naloxone have been fully investigated in human
sion. Buprenorphine pharmacology and its complex interac-
tions at the 
affinity for various opioid receptors (it is an agonist at the
-opioid receptor),61 its effect at the 
-opioid receptor is most important for respiratory depres-
sion. Buprenorphine pharmacology and its complex interac-
tions with naloxone have been fully investigated in human
volunteers in a recent series of studies in our laboratories in
Leiden.11,41,45 Although buprenorphine induces significant
respiratory depression at clinical doses, respiratory depres-
sion exhibits an apparent maximum or ceiling effect typical
for a partial agonist at the 
-opioid receptor.15 However, the
potential benefit of a ceiling effect in the side-effect profile
of buprenorphine is counteracted to some extent by its resis-
tance to naloxone-induced reversal.41 In a naloxone dose-
response study in human volunteers, reversal of intravenous
buprenorphine (0.2 mg) with standard doses of intravenous
naloxone (up to 0.8 mg) had no effect. Increasing the dose of
buprenorphine (0.2 mg) with standard doses of intravenous
naloxone (5–7 mg) caused a decline in reversal activity.
Therefore, the full dose-response relationship was bell
shaped, as shown in figure 4. A bell-shaped dose-response
relationship has also been observed for other buprenorphine-
duced actions.51 These data indicated that reversal of bu-
prenorphine-induced respiratory depression is possible but
depends on the dose of naloxone and its inverse U-shaped
dose-response relationship. With the far more rapid biologic
half-life of naloxone, compared with buprenorphine, the
respiratory depressant actions of buprenorphine outlast the
effects of naloxone-induced reversals from bolus injections,
even using higher doses of the reversing agent. A naloxone
regimen consisting of a bolus administration (2–3 mg) fol-
lowed by a continuous infusion (4 mg/h), however, provided
full reversal of buprenorphine within 40–60 min, and this
reversal was sustained.41 A pharmacokinetic-pharmacody-
namic model of buprenorphine-induced respiratory depres-
sion by naloxone has been developed.45 For buprenorphine,
the \( t_{1/2}k_{off} \) was 75 min in the presence of naloxone, dem-
onstrating a similar value to that derived previously in the
absence of naloxone. This slow equilibration is paralleled by
slow receptor association/dissociation kinetics \( t_{1/2}k_{off} = 70 \)
min.55,62 The kinetic values for buprenorphine are in
marked contrast to the rapid kinetics displayed by naloxone
\( t_{1/2}k_{off} = 0.8 \) min, \( t_{1/2}k_{0} = 6.5 \) min.43,45 Hence, reversal of
buprenorphine by naloxone is characterized by the contrast-
ning slow kinetics of receptor site equilibration and receptor
dissociation of buprenorphine with the rapid kinetics of nal-
oxone. This pharmacokinetic/pharmacodynamic model ac-
curately predicts the reversal of buprenorphine by naloxone
up to doses of 4 mg 70 kg \(^{-1}\) h\(^{-1}\), where almost complete
reversal is accomplished. Hence, the pharmacokinetic/phar-
codynamic model provides a good theoretical basis for the
interactions between buprenorphine and naloxone. The
cause for the bell-shaped naloxone-dose response curve in
reversing buprenorphine-induced respiratory depression re-
mains unknown. A possible mechanism may be that bu-
prenorphine acts at two opioid receptor subpopulations, one
mediating the agonist properties at low dose and the other
mediating the antagonistic properties at high dose.11 Alter-
natively, antagonism of the action of buprenorphine at other
opioid receptors, such as the opioid receptor-like 1 receptor,
have been postulated.65

**Naloxone Side Effects**

Early clinical experience in the 1970s suggests that naloxone
use may, under certain specific circumstances, cause serious
and possibly life-threatening side effects, such as pulmonary
edema, cardiac arrhythmias, hypertension, and cardiac ar-
rest.64–68 All the patients described in these case reports were
postoperative patients experiencing (severe) pain and stress.
Even in the most recent prospective study in patients who
were comatose due to opioid overdose, some serious compi-
lcation were seen. Of the 453 patients treated with naloxone,
6 (1.3%) suffered complications such as cardiac arrest,
pulmonary edema, and epileptic seizures,69 with the primary
case of cardiorespiratory complications from naloxone be-
ing a massive release of catecholamines.69 When naloxone is
given to a patient who is hypovolemic, hypotensive, and/or
previously (before opioid treatment) in severe pain or stress,
high-dose naloxone and/or rapidly infused naloxone (i.e.,
not titrated) can cause catecholamine-mediated cardiac arr-
hythmias and vasconstriction. The vasconstriction may
lead to a fluid shift from the systemic circulation to the pul-
monary vascular bed, resulting in pulmonary edema.64
When naloxone is titrated to effect, it is generally safe. Stud-

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![Fig. 4. Bell-shaped naloxone reversal of opioid-induced respiratory depression. Data point are mean values. y-axis: 0 = reversal no better than placebo, 1 = full reversal. Data redrawn, with permission, from van Dorp et al.41](image-url)
ies in animals and healthy volunteers confirm the safety of naloxone use in patients, even at higher doses up to 10 mg or on constant exposure to intermediate to high concentrations of naloxone during 1 to 2 h.41,58

The possibility of cardiovascular complications and re-narcotization (with recurrence of sedation and respiratory depression) should always be anticipated when treating a patient with naloxone. Consequently, cardiorespiratory monitoring is a primary requirement for the patient receiving naloxone, especially when the patient has just received an opioid dose through the intravenous route or is “sympathetically” unstable.

**Reversal of Respiratory Depression by Nonopioids**

For many situations in which respiratory depression is a critical factor in postoperative care, the proper use of naloxone will provide corrective treatment. There is, however, considerable interest and a potential need for improved therapeutic interventions using nonopioid drugs. As discussed earlier, opioid-induced respiratory depression and analgesia are intrinsically linked by their mediation through the μ-opioid receptor. Reversal of opioid-induced respiratory depression by naloxone, therefore, may lead inevitably to the loss of analgesia, which creates difficulties to patient care. Furthermore, in case of a mismatch between the pharmacokinetics and pharmacodynamics of the opioid agonist and antagonist, the possibility for renarcotization may be a cause for concern. Therefore, there may be real therapeutic benefits in adding effective nonopioids to the armamentarium of drugs available for use in the treatment of severe respiratory depression. The remainder of this review will consider some advances and possibilities in the development of nonopioids for the treatment and prevention of respiratory depression.

**5-Hydroxytryptamine (Serotonin, 5HT) Receptor Ligands**

Respiratory drive is controlled by key centers in the brainstem (fig. 5), such as the rhythm-generating pre-Bötzinger complex that receive modulating inputs from the cortex and from central and peripheral chemoreceptors. The inhibition of this dynamic respiratory control system by opioids has been reviewed recently.70 Respiratory drive may be restored by manipulation of neuronal transmitter systems in those regions, particularly serotonergic systems. 5HT enhances activity in respiratory neurons primarily through actions at 5-HT1A (sometimes referred to as 5HT1A/7 or 5HT1-like), 5HT2, and 5HT4 receptors.71 5HT-based approaches, unlike opioid antagonists, do not usually demonstrate any antagonism of opioid-induced analgesia.

**5HT1A and 5HT7 Receptor Agonists.** Perhaps, key to consideration of the development of new 5HT receptor ligands in respiratory depression is their actions at the pre-Bötzinger complex, an area of the ventrolateral medulla (identified in animals but not to date in humans) that generates respiratory rhythm.72–74 Although there are mixed reports in the literature of the effects of 5HT1A agonists on respiratory function, more recent studies in a variety of animal species in vivo and in vitro seem to show that administration of 5HT1A agonists, such as 8-hydroxy-2-(di-n-propylamino)tetralin (8-OH-DPAT) or the partial agonist buspirone, reverse opioid-induced respiratory depression without affecting antiinociception.75–79 It is thought that enhancement of synaptic inhibition within the pre-Bötzinger complex may be a key site of action of 8-OH-DPAT and buspirone.80–83 However, respiratory centers in the brainstem also receive modulatory input from other brain areas, which may also be affected by opioids and 5HT1A agonists. Medullary raphe neurons, for example, may also be important in determining the overall effects on respiratory depression.70,84–86 Medullary raphe neurons project to respiratory centers, and activation of 5HT1A receptors on raphe neurons may contribute significantly to respiratory restoration by modulating central...
expiratory neurons and spinal motoneurons.\(^{84-86}\) 5HT\(_{1A}\) receptor influence affects many of the complex constituent mechanisms that together determine respiratory outcome and its manifold expressions such as breathing rate, tidal volume, hypoxic ventilatory response, \textit{etc.}, including an influence on related and interacting components such as the cardiovascular system.\(^{77}\)

One difficulty in interpreting the effects of 5HT ligands in terms of actions at individual 5HT receptors is frequently that many of the ligands available do not demonstrate a high enough degree of selectivity to enable a clear derivation of the effect of that ligand among the overall plethora of 5HT receptors (13 5HT receptors are acknowledged in the recent receptor classification review).\(^{87}\) Such is the case with 8-OH-DPAT, which has a high affinity for both 5HT\(_{1A}\) and 5HT\(_{7}\) receptors. Because buspirone is not an agonist at 5HT\(_{7}\) receptors but has similar actions to 8-OH-DPAT on respiratory systems, there is a tendency to equate the actions of 8-OH-DPAT with 5HT\(_{1A}\) receptors. However, the potential of the importance of 5HT\(_{7}\) receptors in the pre-Bötzinger complex and in the pulmonary vasculature should not be overlooked and ligands with greater selectivity are clearly required to resolve the contributions of 5HT\(_{1A}\) and 5HT\(_{7}\) receptors.\(^{70,76}\) A further restriction of the available 5HT\(_{1A/7}\) receptor ligands is that an even fewer number of compounds are licensed for study in humans. Buspirone may be used clinically, and there are anecdotal clinical reports of buspirone improving respiratory dysfunction, for example, postoperatively after removal of an astrocytoma, in Rett syndrome and after a brainstem infarction.\(^{88-91}\) However, in a double-blinded, placebo-controlled crossover study in 12 healthy volunteers, buspirone (60 mg orally) failed to demonstrate reversal of morphine-induced respiratory depression (30 mg/70 kg intravenously).\(^{91}\) From our earlier discussions with regard to the use of opioid antagonists for reversal of respiratory depression, any study of this kind must take into consideration both pharmacokinetic and pharmacodynamic considerations. This is discussed by the authors of the buspirone study in healthy volunteers who, using nonparametric pharmacokinetic/pharmacodynamic modeling with the available data on buspirone, concluded that, in this study, the effect-site concentrations of buspirone achieved in the brain were lower than those estimated in studies with rats.\(^{88}\) The inability of buspirone to reverse morphine-induced respiratory depression, therefore, may be due to inadequate buspirone dosing. However, higher doses of buspirone were contraindicated because, in the healthy volunteers, buspirone (60 mg) significantly increased morphine-induced nausea.\(^{91}\) Therefore, buspirone would not seem to be an adequate clinical tool to treat opioid-induced respiratory depression or to explore 5HT\(_{1A}\) mechanisms in man.

5HT\(_{4a}\) Receptor Agonists. 5HT\(_{4a}\) receptors are also expressed on neurons of the pre-Bötzinger complex and are coexpressed with opioid \(\mu\)-receptors.\(^{92-94}\) 5HT\(_{4a}\) agonists do not influence opioid-induced analgesia because 5HT\(_{4a}\) receptors are absent from pain-processing regions.\(^{94}\) Stimulation of 5HT\(_{4a}\) receptors in the pre-Bötzinger complex in rats by the agonist BIMU8 has been shown to protect spontaneous respiratory activity and to reduce or abolish fentanyl-induced respiratory depression.\(^{92}\) In another species, the goat, an alternative 5HT\(_{4a}\) agonist, zacopride, reversed etorphine-induced respiratory depression without affecting immobilization or sedation.\(^{76}\) The functional antagonism of opioids and 5HT\(_{4a}\) agonists on rhythms in the pre-Bötzinger complex are thought to be due to convergence of neuronal signaling due to their opposite effects on cyclic adenosine monophosphate; stimulation of \(\mu\)-opioid receptors resulted in a decrease in cyclic adenosine monophosphate and decreased inspiratory drive, whereas stimulation of 5HT\(_{4a}\) receptors induced an increase in cyclic adenosine monophosphate and increase in inspiratory drive.\(^{92,94}\)

To investigate the potential clinical benefits of 5HT\(_{4a}\) agonists in man, the 5HT\(_{4a}\) agonist mosapride has been investigated in a double-blinded, crossover study in healthy volunteers.\(^{95}\) Twelve healthy volunteers received oral doses of mosapride (5 mg daily for 5 days), and on the day of testing, three doses of mosapride (5 mg) were administered at 90-min intervals, the second dose was administered concomitantly with morphine (15 mg/70 kg), with a similar dose of morphine being further administered within 2 h. Mosapride had no effect on the respiratory depression induced by morphine. As with the similar clinical study with buspirone in healthy volunteers,\(^{94}\) a pharmacokinetic/pharmacodynamic model showed that the negative results with mosapride may be attributable to the low potency and/or limited central effect-site concentrations of mosapride being achieved in the clinical study compared with the study in the rat.\(^{95}\) However, both the buspirone and mosapride studies show the value of pharmacokinetic/pharmacodynamic modeling in the interpretation of early clinical data, and neither study should prevent future clinical possibilities of 5HT\(_{1A/7}\) or 5HT\(_{4}\) receptor agonists from being considered.

**Ampakines**

In recent years, there has been considerable development in our understanding of the role of the excitatory glutamatergic transmitter system and of glutamatergic dysfunction in the central nervous system. Much of that focus has been directed toward pharmacological blockade of the \(N\)-methyl-\(d\)-aspartate receptor, but for many clinical impairments, metabotropic glutamate receptors and particularly modulators of the \(\alpha\)-amino-3-hydroxy-5-methyl-4-isoxazole-proprionic acid (AMPA, fig. 6) receptors seem to offer interesting prospects.\(^{96}\) AMPA receptor modulators do not bind directly to the glutamate binding site but to an allosteric pocket within the receptor complex that allows the modulator to augment the function of the activated AMPA receptor but has no intrinsic activity itself at the receptor. At first sight, one essential difficulty of this approach to drug development may be the ubiquitous nature of glutamatergic transmission within the central nervous system, leading to a general enhancement of excitatory activity with little opportunity to...
achieve drug-induced selective actions. However, it seems that AMPA receptor structure is not uniform across the brain, and AMPA modulation may operate within specific malfunctioning areas without leading to generalized behavioral activity or widespread excitotoxicity, thereby enabling improvement in specific disorders of impaired neuronal glutamnergic function, such as cognitive disorders, attention deficit hyperactivity disorder, and schizophrenia.97,98 This may extend to actions to improve respiratory depression. Within the pre-Bötzingher complex, AMPA receptors are important for maintaining rhythmicity,99,100 and hence, blockade of AMPA sites results in an inhibition of respiration and their enhancement leads to increases in respiratory frequency.99 Several distinct classes of positive AMPA receptor modulators have been described including aniracetam, benzothiadiazides, and related 7-chloro-3-methyl-3– 4-dihydro-2H-1,2,4 benzothiadiazine S,S,-dioxide and 2,6,7-trioxo-1-phosphabicyclo[2.2.2.]octane-4-methanol-1-oxide compounds, biarylsulfonides (LY392098 and others), but the most interesting to date seem to be a group of benzamides (fig. 6), collectively called ampakines, examples of which are CX516, CX546, CX614, and CX717.96,101 The AMPA receptor is composed of arrangements of receptor subunits, and different ampakines may show subunit preferences allowing differentiation of their modulatory actions; positive enhancement of AMPA receptors by CX516 is by increase in the amplitude of synaptic responses, while that of CX546 is by prolongation of the duration of synaptic action and CX516 accelerates channel opening, whereas CX546 primarily slows channel closing.102 CX546 binds to the AMPA receptor complex at an allosteric site within the AMPA receptor complex in its agonist bound state, not to its desensitized or agonist-free state, and modulates the kinetics of deactivation and desensitization.102–104 CX614 is closely related to CX546 but is more sterically hindered and has been used to further define the allosteric binding site and actions of the ampakines.105 Actions within the pre-Bötzingher complex, probably underlie the observed actions of CX546 and CX717 to reverse the opioid-induced inhibition of respiratory drive in medullary slice and brainstem-spinal cord preparations in vitro and plethysmography in vivo in the rat, without antagonizing fentanyl-induced antinociception (fig. 7).106,107 Hence, in the rat, the ampakines CX546 and CX717 act as a powerful stimulant of respiratory frequency and tidal volume after respiratory depression induced by opioid μ-receptor agonists.

To date, most testing on ampakines has been done in animals. A placebo-controlled pilot study of the related ampakine CX516 combined with clozapine in schizophrenia demonstrated the drug to be well tolerated and was associated with improvements in attention and memory.108 In a preliminary report, German researchers showed improvement of respiratory rate by the oral administration of a single dose (1500 mg) CX717 but not hypercapnic minute venti-

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Fig. 6. Chemical structures of (A) α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA), (B) benzamide, and (C) CX614.

Fig. 7. Effect of the ampakine CX717 on fentanyl-induced respiratory depression in the adult rat. (A) A measure of 60 μg/kg intravenous fentanyl followed by 15 mg/kg intravenous CX717 approximately 6 min after the fentanyl infusion. (B) Pretreatment with CX717 (15 mg/kg intravenous) followed by 60 μg/kg intravenous fentanyl. Data are population means with 9 to 10 animals per group. Data redrawn, with permission, from Ren et al.107

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loration during low-dose alfentanil infusion without affecting antinociception.‡

Minocycline, a Microglial Inhibitor

A further action of the ampakine CX546 is the enhancement of astrocyte metabolism, which increases glucose use and lactate production and may play some role in cognition enhancement.109 With regard to respiratory depression, however, the action of opioids on immune cells such as astrocytes and microglia may represent a further novel target for drug development. Opioid activation of the immune system may act as a homeostatic mechanism to switch off analgesia mediated within the central nervous system by the release of endogenous opioids to nociceptive stimuli.110 Conversely, inhibitors of glial activation have been shown to enhance the analgesic efficacy of acute and chronic morphine.111 A recent study has investigated whether minocycline, a tetracycline-derivative and an inhibitor of microglial activation,112 may also influence opioid-induced respiratory depression as well as analgesia in rats.113 In agreement with general expectations, minocycline enhanced antinociception induced by morphine (this effect is independent of its antimicrobial properties). Furthermore, using full body plethysmography and pulse oximetry, minocycline was shown to attenuate the respiratory depressant effects of morphine on measures such as tidal volume, minute volume, inspiratory and expiratory forces, and blood oxygen saturation, although minocycline did not affect respiratory rate.113 Unusually, therefore, the same doses of minocycline demonstrated opposing effects on opioid-induced analgesia and respiratory depression in the rat, enhancing the former while suppressing the latter. The apparent inhibition of tidal volume and other measures, but not respiratory rate, is speculated to arise from glial activation mechanisms in brain areas that are involved primarily in control of tidal volume, such as neurons of the pontine respiratory group (nucleus parabrachialis medialis and Kolliker-Fuse nucleus), but not in areas involved in respiratory frequency, such as the pre-Bötzinger complex.113 Hence, minocycline suggests an interesting possibility for the development of inhibitors of glial activation for reversal or prevention of opioid-induced respiratory depression that may simultaneously enhance opioid-induced analgesia and offer a site of action different from that hypothesized for the 5HT receptor agonists or ampakines.

Conclusion

There is ample evidence that opioid analgesics interact with ventilatory control, causing some degree of respiratory depression.7,8,114,115 However, opioid treatment of moderate to severe pain is generally safe with about 0.5% or less events related to respiratory depression. However, there are still fatal outcomes of opioid analgesic use even under controlled conditions in the clinical settings often related to opioid overdose-related respiratory depression.115 The only treatment currently available to reverse opioid respiratory depression is by direct antagonism of the site of action of opioid effect, the μ-opioid receptor, using intravenous naloxone. Naloxone use is effective although its efficacy depends on many factors and includes the pharmacokinetics and pharmacodynamics (including receptor kinetics) of the opioid analgesic, which requires antagonism. Because of the relative short elimination half-life of naloxone, the clinical approach to severe opioid-induced respiratory depression would be to titrate naloxone to effect and subsequently continue treatment by continuous infusion until chances for renarcotization have diminished. New treatments and/or approaches to prevent opioid respiratory depression without affecting analgesia have led to the experimental application of new agents such as serotonin agonists, ampakines, and the antibiotic minocycline. Lacking so far are controlled human trials showing efficacy to treat high-dose opioid toxicity. There are other promising agents available that deserve study, for example, inhibitors of the sodium/proton exchanger type 3 (NHE3) that have a stimulatory effect on breathing due to an action within central respiratory pathways.116,117

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Anesthesiology, V 112 • No 1 • January 2010


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