Opioid-induced respiratory effects: new data on buprenorphine

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When selecting the appropriate long-acting opioid to treat cancer pain, both analgesic efficacy and safety need consideration. Generally, opioids are well tolerated. However, of opioid-typical adverse events, respiratory depression is especially important because of the risk of a fatal outcome. Although all potent opioid analgesics act via the µ-opioid receptor system, they differ in how they affect respiratory control. Recently, the respiratory effects of fentanyl (1–7 µg/kg) and buprenorphine (0.7–9 µg/g/kg) were compared in healthy opioid-naïve volunteers. Fentanyl produced dose-dependent depression of respiration with apnoea at doses ≥3 µg/kg, while buprenorphine caused depression that levelled at ~50% of baseline with doses ≥2 µg/kg. These findings indicate the occurrence of a ceiling in the respiratory depression induced by buprenorphine but not by fentanyl. Surprisingly few studies have addressed the clinically important ability to reverse the respiratory effects of opioids. A recent assessment of the naloxone dose required to reverse 0.2 mg intravenous buprenorphine-induced respiratory depression in healthy opioid-naïve volunteers, found that the accumulated naloxone dose causing 50% reversal of respiratory depression was 1.20 ± 0.32 mg/70 kg (given in 30 min); 80% reversal was observed at 2.50 ± 0.60 mg/70 kg (given in 30 min). At greater buprenorphine doses, full reversal is observed when the duration of naloxone infusion is increased. These findings indicate the need for a continuous rather than bolus administration of naloxone to reverse the respiratory effects of buprenorphine. In conclusion, buprenorphine is more favourable compared with fentanyl in respect to ventilatory control. Buprenorphine causes limited respiratory depression with a ceiling effect at higher doses, while fentanyl causes dose-dependent respiratory depression with apnoea at high dose levels. In the rare instance of respiratory depression, reversal is possible with a sufficient and continuous infusion of naloxone. Palliative Medicine 2006; 20: s3–s8

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Introduction

Long-acting opioids are important analgesics for the treatment of cancer pain but are variable in terms of analgesic efficacy and safety. Although opioids are generally well tolerated, consideration of safety is needed because – in addition to analgesia – morphine and most other opioids produce their characteristic responses both centrally and peripherally. Of opioid-typical adverse events, respiratory depression is the most serious because of the risk of a fatal outcome for the patient. The mechanism of opioid-induced respiratory depression is µ-opioid receptor inhibition of the brainstem respiratory control centres. Opioids affect both the rate and depth of respiration, eventually resulting in an increased arterial partial pressure of carbon dioxide and reduced partial pressure of oxygen. Data from studies in mice indicate that the desired (antinociceptive) and undesired (respiratory depression) effects of morphine (and its active metabolite morphine-6-glucuronide) and probably all µ-opioids are linked to the same target: the µ-opioid receptor gene (Oprm). Mice with intact µ-opioid receptors showed a dose-dependent decrease in both breathing frequency and tidal volume. However, no such effect was observed in mice lacking the µ-opioid receptor (so-called µ-opioid receptor knockout mice). Similarly, mice with µ-receptors showed dose-dependent antinociception from morphine, while no effect was observed in µ-opioid receptor knockout mice (see also Figure 1). Clinical studies in volunteers and patients on the effect of morphine on respiration have also shown a dose–response relationship. For example, morphine causes a dose-dependent decrease in minute ventilation of 6–7 L/min before the drug is given to unstable and cyclic breathing with both a reduction in the breathing frequency and the depth of breathing at 0.2–0.3 mg/kg. At higher doses apnoea may occur when morphine is given to persons without pain.
In this short review I will discuss the respiratory behaviour of an opioid that is frequently used in the treatment of pain, buprenorphine. It is a potent opioid with special characteristics. I will (i) compare buprenorphine and fentanyl dose-(respiratory) response curves; (ii) compare buprenorphine’s analgesic and respiratory responses; and (iii) discuss the ability of naloxone to reverse buprenorphine-induced respiratory depression.

Respiratory depression: buprenorphine versus fentanyl

Recent data from published case studies have indicated a number of instances where patients have suffered severe respiratory depression after the continuous infusion of fentanyl via a transdermal patch. To underline the importance of this issue, of six case patients who presented with drug-induced respiratory depression, two died. We relate these serious adverse events to (1) the relatively high doses of fentanyl given; (2) the periodic nature of pain; (3) psychomimetic comedication (such as sedatives, alcohol, other pain medication) and (3) the absence of supervision of the patients. But do all opioids behave in the same way? Our group attempted to answer this question by investigating the comparative effects on respiratory depression of the equipotent analgesics fentanyl and buprenorphine in rats. Fentanyl injected intravenously into animals up to a dosage of 0.09 mg/kg showed a dose-dependent linear increase in arterial pressure of carbon dioxide, a surrogate measure of respiration (Figure 2). On increasing the fentanyl dosage further, the animals died of fatal respiratory depression. In contrast, when buprenorphine was administered intravenously there was an initial increase in arterial pressure of carbon dioxide, which rapidly levelled off even on increasing the dosage up to 3.0 mg/kg (Figure 2). This phenomenon, known as the ceiling effect, represents the point where the agonistic effects of buprenorphine plateau and the drug develops an action more akin to that of an antagonist, thereby limiting respiratory depression.

How do buprenorphine and fentanyl compare in respect to respiratory depression in humans? We conducted a double-blinded, placebo-controlled study of
fentanyl and buprenorphine in 48 volunteers. Using the computer-steered 'dynamic end-tidal forcing' technique, respiratory studies were performed at a clamped end-tidal oxygen (15 kPa) and carbon dioxide (7 kPa) tension. Ventilation was measured for up to 7 hours. Dose–response relationships were observed with fentanyl in the range of 0–9 µg/kg and for buprenorphine at 0–7 µg/kg (with respect to analgesia fentanyl and buprenorphine are equipotent relative to morphine). Fentanyl caused dose-dependent reduction of minute ventilation with respiratory instability at doses of 3 µg/kg and greater. In one subject, prolonged periods of apnoea were observed at the highest dose tested (500 µg in a 70 kg volunteer). Buprenorphine similarly caused dose-dependent reduction of minute ventilation, however, in contrast to fentanyl a plateau in respiratory depression (about 50% of baseline) occurred at dosages ≥3 µg/kg (see also Figure 3). Importantly, no respiratory instability, periodic breathing or apnoea occurred, even at the highest dose tested (600 µg in a 70 kg volunteer).

**Buprenorphine: ceiling in respiration but not in analgesia**

An important question is whether the ceiling in respiratory depression is linked to a concomitant reduction in analgesia. This question was investigated using a standard electric pain model with two groups of patients, each receiving a different dosage of buprenorphine (3 and 6 µg/kg). The results demonstrated that doubling the

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**Figure 3** Effect of increasing doses of fentanyl and buprenorphine on respiration in human volunteers (n=5–8 per dose group; n=1 for the highest fentanyl dose). Note the dose-dependent decrease for both drugs with apnoea at high-dose fentanyl but a ceiling or plateau at intermediate to high dose buprenorphine. Values are population mean. For clarity no error bars are shown. Data are adapted from Dahan et al.

**Figure 4** Effect of two doses of buprenorphine (3 µg/kg cyan dots; 6 µg/kg grey dots) on respiration (left) and analgesia (right) in human volunteers (n=10 per dose group). Note that doubling the dose had no further effect on respiration while analgesic efficacy increased significantly. For clarity no error bars are shown. Data are adapted from Dahan et al.
Figure 5 Influence of naloxone on buprenorphine-induced respiratory depression. Examples of four volunteers that received 0.2 mg buprenorphine intravenously from \( t = 2 \) to \( t = 62 \) min, followed by various doses of naloxone from \( t = 32 \) to \( t = 62 \) min. Note that at low doses of naloxone (0.5 and 1.0 mg) no reversal occurs while at doses of 2 mg and greater full reversal is observed. Each dot represents a 1-min average. The broken line is baseline ventilation (predrug ventilation). The thick black lines are the infusion periods of buprenorphine and naloxone.

**Reversal of buprenorphine-induced respiratory depression using naloxone**

Knowledge of the ability to reverse opioid-induced respiratory depression is important for all potent and clinically used opioids (eg, fentanyl, morphine, buprenorphine). However, there are surprisingly few studies that have addressed the reversal of opioid-induced respiratory effects. Despite data from early studies to the contrary, \(^{18,19}\) we performed a study investigating the reversal of the effects of buprenorphine on respiratory function with naloxone in humans.\(^{20}\) An adaptive trial design was used to find the dose that caused full reversal of buprenorphine-induced respiratory depression. Twenty-one opioid-naïve volunteers were tested over a 90-min period with end-tidal carbon dioxide tension clamped at 7 kPa. Buprenorphine 0.2 mg/kg was administered as a continuous intravenous infusion for 1 hour. After a period of 30 min from the start of buprenorphine infusion, either placebo (NaCl 0.9%, \( n = 7 \)) or naloxone (0.5–5 mg, \( n = 14 \)) was infused for 30 min, and the effect on breathing assessed for a further 30-min period afterwards. As expected, placebo did not affect the buprenorphine-induced decrease in ventilation rate during the period 0–60 min. A slow decline in ventilation rate was observed, reaching a nadir of depression after 70 min. On infusing low-dose naloxone (0.5 mg) over 30 min there was little discernible effect on buprenorphine-induced respiratory depression following initial naloxone injection, leading to a continued depression (Figure 5). At such a low dose it is relatively difficult
for naloxone to displace buprenorphine already bound to μ-opioid receptors. However, on increasing the dosage of naloxone to 2 mg, a full reversal of the respiratory effect was observed, returning ventilation to its baseline level (Figure 5). Thus, total reversal of respiratory depression induced by buprenorphine can be brought about at a relatively low dose of continuously infused naloxone.

The data show that full reversal of respiratory depression produced by buprenorphine can be achieved by using a continuous infusion of sufficiently high dosages of naloxone. The dose-dependent reversal of buprenorphine-induced respiratory effects follows a sigmoidal relationship (Figure 6): 50% reversal of depression is achieved after 30 min of continuous infusion of naloxone 1.2 ± 0.32 mg/70 kg, and 80% reversal with 2.50 ± 0.60 mg/70 kg. Reversal of greater doses of buprenorphine was recently studied in our laboratory (Dahan, unpublished observation) and – not surprisingly – we observed that not greater doses of naloxone are needed for reversal but a longer infusion duration is needed. In this respect buprenorphine behaves similar to other potent and long-acting opioids with high affinity at the μ-opioid receptor.

Conclusions

In summary, buprenorphine compares favourably with fentanyl in respect to ventilatory control. Unlike fentanyl, which causes dose-dependent depression with apnoea at high dosage, buprenorphine causes limited respiratory depression with a ceiling effect at high dosages. In the rare instance of respiratory depression with buprenorphine, full reversal using a continuous infusion of naloxone to obtain a constant (and sufficient) plasma concentration is possible.

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References

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