Buprenorphine Induces Ceiling in Respiratory Depression but Not in Analgesia

Buprenorphine is a semi-synthetic opioid in clinical use for treatment of acute and chronic pain since 1979. Buprenorphine is a potent analgesic with agonistic activity at the µ-opioid receptor and antagonistic properties at the κ-opioid receptor. Human studies show that buprenorphine behavior is typical of µ-opioid receptor agonists, with respect to its intended effect (potent and long-lasting analgesia) and side effects (for example sedation, nausea, delayed gastric emptying and respiratory depression). In a previous study, in a group of healthy volunteers buprenorphine-induced respiratory depression demonstrated ceiling (or an apparent maximum effect) at doses > 0.1 mg (per 70 kg). Ventilation at a fixed end-tidal PCO\textsubscript{2} reached maximum peak depression of about 50% of baseline. Buprenorphine’s behavior contrasts that of fentanyl, which showed irregular breathing and apnea at high dose (> 200 µg per 70 kg). These findings suggest a greater margin of safety for buprenorphine relative to other potent opioids frequently used to treat severe acute and chronic pain. However, buprenorphine’s safety profile must be considered against the background of its analgesic profile. For example, would ceiling in respiratory depression coincide with ceiling in analgesia then the value of buprenorphine would be limited in clinical practice. Recently we observed in rats the occurrence of ceiling in buprenorphine’s respiratory effect while no ceiling was observed in buprenorphine’s antinociceptive behavior. There are no good experimental human studies available on buprenorphine’s analgesic behavior at doses causing ceiling in respiratory effect. To address this important issue we assessed the effect of two doses of intravenous buprenorphine (0.2 and 0.4 mg/70 kg) on respiration and analgesia in a group of young and healthy volunteers. Previous studies indicated that the respiratory effect of 0.2 and 0.4 mg buprenorphine have similar and limited respiratory effects.

Methods

Twenty volunteers (10 men, 10 women; aged 22–35 years, weight 62–92 kg) participated in the protocol after approval was obtained from the local Human Ethics Committee. All subjects were healthy and did not have a history of illicit substance abuse or smoking. They were asked to refrain from stimulants and depressant substances for at least 12 h before the study. Each subject participated once. After arrival in the laboratory the subjects were familiarized with the pain test and breathing apparatus for about 60 min.
Half of the subject group \((n = 10, 5 \text{ men}, 5 \text{ women})\) received 0.2 mg (per 70 kg) buprenorphine i.v., the other half 0.4 mg (per 70 kg) buprenorphine i.v. Buprenorphine (Reckitt Benckiser Healthcare Ltd, Hull, UK) was infused slowly over 90 s.

**Respiration**

To study ventilation we used the dynamic end-tidal forcing technique. This technique enables us to force end-tidal PCO\(_2\) \((P_{ET}CO_2)\) and end-tidal PO\(_2\) \((P_{ET}O_2)\) to follow a specific pattern in time. In this study we clamped the \(P_{ET}CO_2\) and \(P_{ET}O_2\) to 7 kPa and 14.5 kPa, respectively, throughout the studies. The subjects were comfortably positioned in a hospital bed and breathed through a face mask, positioned over nose and mouth (a nose clip was not used). The face mask received fresh gas (45 l.min\(^{-1}\)) from a gas mixing system consisting of three mass flow controllers (Bronkhorst High-Tech BV, Veendendaal, The Netherlands) for the delivery of oxygen, carbon dioxide and nitrogen. A personal computer provided control signals to the mass flow controllers allowing the adjustment of the inspired gas concentrations to obtain the desired end-tidal concentrations. The in- and expired gas flows were measured at the mouth using a pneumotachograph connected to a pressure transducer (Hans Rudolph, Wyandotte, MI, USA) and electronically integrated to yield a volume signal. The volume signal was calibrated with a motor-driven piston pump. The oxygen and carbon dioxide concentrations were measured using a gas monitor (Multicap, Datex, Helsinki, Finland); a pulse oximeter (Masimo, Irvine, CA, USA) continuously measured the oxygen saturation \((\text{SpO}_2)\) of arterial hemoglobin with a finger probe. All relevant variables (minute ventilation, \(\text{SpO}_2, P_{ET}CO_2\) and \(P_{ET}O_2\)) were available for on-line analysis and stored on a breath-to-breath basis for further analysis.

At several times respiration was measured: \(t = -30\) min (30 min before the drug was infused) and at times \(t = 15, 75, 140, 180, 240, 300, 360, 420\) and 480 min after the infusion of buprenorphine. The respiratory studies started after ventilation (at a fixed \(P_{ET}CO_2\) of 7 kPa) had reached a steady state. Next the mean value of 10 consecutive breaths was calculated and used in the data analysis. Generally no more than 7 minutes were needed before a measurement at steady state was obtained. In between respiratory measurements the subjects were taken off the mask and analgesia testing was performed.

**Analgesia**

Acute pain was induced by an electrical current through two surface electrodes (Red Dot, 3M, London, Ontario, Canada) placed on the skin overlaying the tibial bone (shin bone) of the left leg. The electrodes were attached to a computer interfaced current stimulator (CICS, Leiden University Medical Center, Leiden, The Netherlands). The intensity of the noxious stimulation was increased from 0 mA in steps of 0.5 mA per 1 s. The stimulus train consisted of a square-wave pulse of 0.2 ms duration applied at 10 Hz and had a cutoff at 128 mA. The subjects were instructed to press a button on a control panel when no further increase in stimulus intensity was acceptable (pain tolerance). Upon pressing the pain tolerance button, the stimulus train ended. This procedure was performed three times prior to drug infusion (the
mean of which was used as baseline value) and at fixed times after drug infusion (at times $t = 5, 10, 45, 80, 110, 130, 165, 210, 270, 330, 390, 450$ and $490$ min after the drug infusion). The current at which pain tolerance occurred was automatically collected and stored on the hard disc of a computer for further analysis. The involvement of the observers in the pain assessments was restricted to training the subjects and to the initiation of the stimulus train during the studies.

**Data Analysis**
Data analysis was performed on the absolute respiration and pain tolerance values and on the values relative to baseline (**i.e.,** $\Delta$ventilation and $\Delta$pain tolerance). Data are reported as mean (SD). Statistical analysis was performed using SigmaStat 3.1 (Systat Software, Inc., Point Richmond, CA, USA). A two-way repeated measures analysis of variance was applied to detect a significant difference of buprenorphine dose on respiration or analgesia and to detect whether sex differences were present. *Post-hoc* analysis was by *t*-test. *P*-values $< 0.05$ were considered significant.

**Results**
All subjects completed the study without major side effects. Most prominent side effects were nausea and vomiting that occurred in $80\%$ and $40\%$ of subjects, respectively. Nausea/vomiting remained untreated throughout the study period.

**Respiration**
The two buprenorphine doses had a similar effect on ventilation. Baseline ventilation at a $P_{ET}CO_2$ of $7$ kPa did not differ between the two dose groups: $24.2$ (2.3) l.min$^{-1}$ in the $0.2$ mg versus $23.5$ (1.9) l.min$^{-1}$ in the $0.4$ mg buprenorphine group. After infusion of the drug ventilation showed a rapid decline and reached peak depression between $t = 150$ and $180$ min (see figure 1). This effect was dose-independent with respect to timing and magnitude: at peak respiratory depression ventilation was $13.1$ (1.8) l.min$^{-1}$ (0.2 mg) versus $12.0$ (1.3) l.min$^{-1}$ (0.4 mg, n.s.). The overall effect of buprenorphine on ventilation was dose-independent over the $8$ hours of the study: $0.2$ *versus* $0.4$ mg, $P > 0.05$. No sex difference was observed (factors sex and the interaction term between sex and dose, $P > 0.05$).

**Analgesia**
A significant increase in analgesia was observed going from $0.2$ to $0.4$ mg buprenorphine. Baseline pain tolerance currents did not differ between the two groups: $16.3$ (3.9) mA (0.2 mg) *versus* $15.0$ (2.6) mA (0.4 mg) (n.s.). At $0.2$ mg buprenorphine a small short-lived analgesic effect was observed with a maximum increase in pain tolerance current of $6.7$ (2.8) mA occurring at $t = 75$ min (figure 2). Peak analgesic effect was $41\%$ above baseline current. In contrast, $0.4$ mg buprenorphine caused a large and long-lived analgesic effect with a maximum increase in pain tolerance current of $23.8$ (7.4) mA occurring at $t = 130$ min.
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Figure 1. Influence of intravenous buprenorphine, 0.2 and 0.4 mg (per 70 kg), on inspired minute ventilation at a fixed $P_{ETCO_2}$ of 7 kPa in healthy volunteers (each dose: $n = 8$). The influence of the two buprenorphine doses is similar with respect to peak respiratory depression and duration of effect.

Figure 2. Influence of intravenous buprenorphine, 0.2 and 0.4 mg (per 70 kg), on pain tolerance in healthy volunteers (each dose: $n = 8$). Values are the increase in currents to achieve pain tolerance relative to baseline pain tolerance currents. A significant increase in analgesia is observed going from 0.2 to 0.4 mg buprenorphine.
Peak analgesic effect was 159% above baseline current ($P < 0.01$ versus 0.2 mg). The overall effect of buprenorphine on analgesia was dose-dependent over the 8 hours of the study (0.2 versus 0.4 mg, $P < 0.01$). No sex difference was observed (factors sex, sex $\times$ dose, $P > 0.05$).

**Discussion**

In the current study we examined the effect of 0.2 and 0.4 mg intravenous buprenorphine (dosed per 70 kg) on ventilation and on analgesia in healthy volunteers. We observed that doubling the dose of buprenorphine increased its peak analgesic effect by a factor of 3.5 (from 6.7 mA to 23.8 mA). In contrast, the timing and magnitude of respiratory depression remained unchanged by doubling the buprenorphine dose (compare figures 1 and 2). These data suggest that buprenorphine displays a plateau for respiratory depression over a dose range where no plateau in analgesic effect is observed. However, before definite conclusions can be drawn our data needs to be viewed in context, that is against the background of a more extensive dose–response relationship. This is important taken into account the observation in some animal studies of a bell-shaped (inverse U-shaped) dose-response relationship for buprenorphine’s analgesic effects.$^8,^9$ In a previous study we assessed the effect of 0.05, 0.1, 0.3 and 0.6 mg buprenorphine on breathing in a similar study population.$^4$ We observed a ceiling effect in peak respiratory depression of the drug at doses $> 0.1$ mg. Although the design of the previous and current studies differs with respect to the duration of measurements (in contrast to the current study, we previously measured breathing continuously for 90 min), we were able to combine these two data sets on peak respiratory depression (figure 3). The continuous line in figure 3 is the data fit using a sigmoid $E_{\text{max}}$ model to all data presented (including the data from the current study). The broken line is the data fit using a decaying exponential model to the complete data set. Both models give similar results, that is, that the 0.3 and 0.6 mg buprenorphine data is on the flat part of the dose–response relationship, about 50% of baseline ventilation. To the best of our knowledge, an extensive dose–response relationship of the analgesic properties of buprenorphine in humans is not available in the literature. We recently assessed the analgesic effect of 0.05, 0.1 and 0.3 mg i.v. buprenorphine over time in 15 healthy young volunteers using our electrical pain model (Dahan, unpublished observation). In figure 4 we plotted the mean increase in current to achieve pain tolerance (relative to baseline pain tolerance current) versus dose and added the data from the current study. A dose-dependent increase in analgesic effect is observed without any sign of ceiling. We believe that this is sufficient proof to state that buprenorphine displays ceiling in respiratory depression over a dose range (0.05–0.4 mg) without causing any ceiling in analgesic effect. Evidently, this is true for the applied acute pain model and the subset of subjects that we used (young and healthy volunteers using no co-medication). Finally, we cannot exclude that ceiling in analgesic effect occurs at greater doses than tested by us.
Figure 3. Human buprenorphine dose–respiratory response (peak respiratory depression) relationship. Values are mean. Open symbols: data from ref. 4; closed symbols: data from the current study. Both a sigmoid $E_{\text{max}}$ model (continuous line) and a decaying exponential model (broken line) were fitted to the data. Both model fits indicate that the 0.3 and 0.6 mg buprenorphine data are on the flat part of the dose–response relationship.

Figure 4. Human buprenorphine dose–analgesic response (peak analgesic effect) relationship. Data are mean. Values are relative to baseline: a value of 1.5 indicates a 50% increase in current to achieve pain tolerance. 0 mg per 70 kg is placebo (0.9% NaCl). Open symbols: data from unpublished observations; closed symbols: data from the current study. To guide the eye a power model was fitted to the data.
**Differential Effect of Buprenorphine on Analgesia and Respiration**

Our data suggest that buprenorphine is a full agonist at μ-opioid receptors (MOR’s) involved in pain processing but a partial agonist at MOR’s involved in respiratory depression. Partial agonism indicates a partial effect despite full MOR occupancy. These findings are in agreement with rat data from our laboratories and with some clinical studies which show the absence of ceiling effect for analgesia (tested at much greater buprenorphine doses than tested by us) and the ability to produce 100% pain relief despite the observation of ceiling for properties other than analgesia (such as sedation and the decrease in respiratory frequency).\(^2,4\)

Buprenorphine behaves very differently from other opioids (full agonists with respect to respiratory effect and analgesia) such as morphine and fentanyl. For example, we previously measured the respiratory depressant effect of morphine simultaneously with morphine’s antinociceptive effects in humans.\(^7\) We observed that over the concentration range that caused a systematic increase in analgesia, morphine caused concentration-dependent respiratory depression without any plateau or ceiling.

It is possible that differences in receptor density may be the cause of the differential buprenorphine effect at the two typical μ-opioid end points studied by us. For example, Garrido et al. showed in rats that progressive MOR knockdown (i.e., the reduction in MOR binding sites) with the irreversible MOR antagonist β-funaltrexamine, caused a marked decrease in alfentanil efficacy.\(^10\) Alfentanil transformed from a full MOR agonist into a partial agonist at reduced MOR availability. It may then be argued that MOR density is greater at pathways in the central nervous system concerned with processing pain than at the respiratory centers in the brainstem.

Another explanation for buprenorphine’s behavior may be found in a difference in the agonist/MOR/G-protein/β-arrestin complex in pain and respiratory neurons. Opioid receptors belong to the superfamily of seven-transmembrane G-protein-coupled receptors which bind to G-proteins and the regulatory protein β-arrestin upon activation.\(^11\) Raehal et al.\(^12\) showed that genetic disruption of the β-arrestin type 2 (βarr2) gene (βarr2 knockout mice) attenuated the respiratory depression (and acute constipation) caused by morphine. In contrast, morphine-induced antinociception was augmented in the βarr2 knockout mice.\(^13\) The authors hypothesized that β-arrestin may play an important G-protein independent role in signal transduction via MOR’s that lead to respiratory depression (and gastrointestinal transit inhibition) but not via MOR’s that lead to analgesia. G-protein independent but β-arrestin dependent activation has been observed for other receptors of the seven-transmembrane receptor superfamily, such as the β2-adrenergic receptor.\(^14\) Following the reasoning of Raehal et al.\(^12\) and taking into account our data, this suggests that MOR activation of a G-protein independent signal transduction pathway is ligand specific: some ligands (such as fentanyl and morphine) cause changes in neuronal physiology fully dependent on G-protein activation causing full MOR responses, while others (such as buprenorphine) activate the β-arrestin protein with diminished responses. We hypothesize that signal transduction due to buprenorphine-activation of MOR’s expressed on respiratory neurons is *via* β-arrestin
mediation and not via G-protein activation. Interestingly, morphine’s active metabolite morphine-6-glucuronide (M6G) displays significantly less respiratory depression than morphine (i.e., a rightward shift of the dose–response relationship). A shared difference in the structure of M6G and buprenorphine with morphine is modification of the hydroxyl group at position C6 of the morphine molecule (morphine: C6–OH, buprenorphine: C6–O–CH₃ and M6G: C6–glucuronide). Possibly this modification at C6 may be the cause for the reduced effect at MOR’s expressed on respiratory neurons (cf. reference 16). Further studies are needed to clarify this important issue.

In contrast to our previous study, we now can address the issue of buprenorphine’s respiratory safety in light of its analgesic properties. Opioid-induced respiratory depression is related to overdosing, concurrent sedation/sleep, co-medication, the periodic nature of pain and underlying disease. The frequency of serious respiratory events related to opioid use remains poorly reported and probably poorly studied. In chronic cancer and non-cancer pain patients, respiratory complications are often erroneously taken for progression of disease and sometimes accepted – and hence unreported – in the light of the poor prognosis of the patient. However, a series of recent case-reports on fentanyl-induced severe respiratory depression and death in old and relatively healthy young patients has lead to several warnings related to the use of fentanyl patches for treatment of chronic pain. The question is whether buprenorphine can make a difference, or – in other words – whether the use of buprenorphine in pain patients will cause less respiratory events than commonly used potent opioids such as morphine and fentanyl. Our data support the notion that since buprenorphine’s respiratory effects are limited, buprenorphine has an advantage over other opioids such as fentanyl and morphine which do not show ceiling at high dose but eventually cause breathing instability and apnea. However, whether this advantage persists under specific conditions such as old age, (lung) disease and use of co-medication needs further study. In opioid-addicts acute co-administration of buprenorphine and benzodiazepines is sometimes associated with fatal respiratory depression.

**Critique of Methods**

We used our pain model as a pharmacological tool and did not intend to simulate clinical (acute or chronic) pain. We previously used this acute pain model (electrical transcutaneous stimulation of the skin) successfully to study the antinociceptive effects of morphine and M6G. The results of these studies were comparable with clinical observations on morphine and M6G pain relief in acute and chronic pain patients with respect to analgesia and drug potency. Since the healthy volunteers tested in our studies were without pain or inflammation, the term antinociception seems a more appropriate description of the opioid behavior in the acute pain test. The choice of the term analgesia throughout this paper was taken – somewhat arbitrarily – to make a distinction from animal studies. In the current study we combined respiratory and analgesia measurements.
Buprenorphine: Respiratory *versus* Analgesic Effects

It may be argued that pain measurement may interfere with respiratory measurements and *vice versa*. This is true, pain testing may have a significant effect on breathing, often causing hyper- and/or hypoventilatory responses due to activation of behavioral respiratory drives;\(^23\) and hypercapnia has been shown to influence pain testing.\(^24\) We tried to minimize the complex interactive effects of pain testing and respiratory measurements by allowing ample time between measurements, but we can not exclude some mutual disturbing effects on both systems.

We were unable to detect significant sex differences in buprenorphine’s respiratory and analgesic responses, although there was a clear trend in the data \((P = 0.09)\) with greater responses in women. Our current study was not designed to examine sex differences, such as observed earlier for morphine.\(^25,26\) *Post-hoc* power analysis indicated that 20 subjects (10 men/10 women) were needed to reveal a sex difference in analgesia after 0.4 mg buprenorphine at the \(P = 0.05\) level.

In conclusion, we tested two incremental intravenous doses of buprenorphine (0.2 and 0.4 mg) on pain relief and respiratory depression in a group of healthy young volunteers. We observed that while buprenorphine’s analgesic effect increased significantly, respiratory depression showed a similar magnitude and timing for the two doses tested. Taking into account additional data from our laboratory we conclude that buprenorphine displays ceiling in respiratory effect but not in analgesic effect over a dose range from 0.05 to 0.4 mg.

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20. US Food and Drug Administration. Safety warnings regarding use of fentanyl transdermal (skin) patches