Buprenorphine induces ceiling in respiratory depression but not in analgesia

A. Dahan1*, A. Yassen2, R. Romberg1, E. Sarton1, L. Teppema1, E. Olofsen1 and M. Danhof2

1Department of Anesthesiology, Leiden University Medical Center, PO Box 9600, 2300 RC Leiden, The Netherlands. 2Leiden/Amsterdam Center for Drug Research, Division of Pharmacology, Gorlaeus Laboratory, Leiden, The Netherlands

*Corresponding author: Anesthesia and Pain Research Unit, Department of Anesthesiology, Leiden University Medical Center (LUMC, P5-Q), PO Box 9600, 2300 RC Leiden, The Netherlands. E-mail: a.dahan@lumc.nl

Background. We measured the effect of two weight adjusted i.v. doses (0.2 mg per 70 kg and 0.4 mg per 70 kg) of the potent opioid buprenorphine on analgesia and respiratory depression in healthy volunteers. The aim of the study was to compare buprenorphine's behaviour with respect to the occurrence of ceiling (or apparent maximum) in these typical µ-opioid protein-(MOP) receptor effects.

Methods. Ten subjects (5 males) received 0.2 mg per 70 kg, 10 others (5 males) 0.4 mg per 70 kg i.v. buprenorphine. Steady-state inspired minute ventilation at a fixed end-tidal \( P_{CO_2} \) of 7 kPa was measured before drug infusion and at regular intervals after drug infusion. Experimental pain was induced using transcutaneous electrical stimulation and a gradually increasing current. Pain tolerance was measured at regular intervals before and after drug infusion. The studies lasted 8 h.

Results. After infusion of the drug ventilation showed a rapid decline and reached peak depression between 150 and 180 min after drug administration. This effect was dose-independent with respect to timing and magnitude. At peak respiratory depression minute ventilation was 13.1 (SD 1.8) litre min\(^{-1}\) in the 0.2 mg group vs 12.0 (SD 1.3) litre min\(^{-1}\) in the 0.4 mg group (n.s.). At buprenorphine 0.2 mg a small short-lived analgesic effect was observed with a maximum increase in pain tolerance current of 6.7 (SD 2.8) mA occurring at 75 min after drug administration. Peak analgesic effect was 29% above baseline current. In contrast, buprenorphine 0.4 mg caused a large and long-lived analgesic effect with a maximum increase in pain tolerance current of 23.8 (SD 7.4) mA occurring at 130 min after drug administration. Peak analgesic effect was 160% above baseline current (0.4 vs 0.2 mg, \( P<0.01 \)).

Conclusions. While buprenorphine’s analgesic effect increased significantly, respiratory depression was similar in magnitude and timing for the two doses tested. We conclude that over the dose range tested buprenorphine displays ceiling in respiratory effect but none in analgesic effect.

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Buprenorphine is a semi-synthetic opioid in clinical use for treatment of acute and chronic pain since 1979. It is a potent analgesic with agonistic activity at the MOP-receptor and antagonistic properties at the KOP-receptor. Human studies show that buprenorphine behaviour is typical of MOP-receptor agonists, with respect to its intended effect (potent and long-lasting analgesia) and side-effects (e.g. it causes 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 \( P_{CO_2} \) reached maximum peak depression of about 50% of baseline. Buprenorphine’s behaviour contrasts that of fentanyl, which showed irregular breathing and apnea at high dose (>100 μg). 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, if the ceiling in respiratory depression coincides with the 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 behaviour.\textsuperscript{4,5} There are no good experimental human studies available on buprenorphine’s analgesic behaviour at doses causing ceiling in respiratory effect. To address this important issue we assessed the effect of two doses of i.v. buprenorphine (0.2 and 0.4 mg per 70 kg) on respiration and analgesia in a group of young and healthy volunteers. Previous studies indicate that 0.2 and 0.4 mg of buprenorphine have similar and limited respiratory effects.\textsuperscript{4}

**Methods**

Twenty volunteers (10 male; aged 22–35 yr, weight 62–92 kg) participated in the study after approval was obtained from the 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 had the mask removed and analgesia testing was performed. The subjects were familiarized with the pain test and breathing apparatus for about 60 s.

Half of the subject group \(n=10\), 5 male) received a weight adjusted dose of 0.2 mg per 70 kg buprenorphine i.v., the other half a weight adjusted dose of 0.4 mg per 70 kg. The 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.\textsuperscript{6} This technique enables us to force end-tidal \(P_{\text{CO}_2}\) (\(P_{\text{E}\text{CO}_2}\)) and end-tidal \(P_{\text{O}_2}\) (\(P_{\text{E}\text{O}_2}\)) to follow a specific pattern in time. In this study we clamped the \(P_{\text{E}\text{CO}_2}\) and \(P_{\text{E}\text{O}_2}\) to 7 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 litre min\(^{-1}\)) from a gas mixing system consisting of three mass flow controllers (Bronkhorst High Tec, Veenendaal, The Netherlands) for 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 inspired and expired gas flows were measured at the mouth using a pneumotachograph connected to a pressure transducer (Hans Rudolf, Myandotta, 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 (Datex Multicap, Helsinki, Sweden); a pulse oximeter (Massimo, Irvine, CA, USA) continuously measured the oxygen saturation (\(S_{\text{PO}_2}\)) of arterial haemoglobin with a finger probe.

**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.\textsuperscript{7} The electrodes were attached to a computer interfaced current stimulator (CICS, Leiden University Medical Center). 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 before drug infusion and the mean used as the baseline value (and at \(t=5, 10, 45, 80, 110, 130, 165, 210, 270, 330, 390, 450\) and 490 min after the drug infusion). The current at which pain tolerance occurred was stored on breath-to-breath basis for further analysis.

Respiration was measured 30 min before the drug was infused \((t=-30\) min) and at times \(t=15, 75, 140, 180, 240, 300, 360, 420\) and 480 min after the infusion of buprenorphine. Respiratory studies were performed after ventilation at a fixed \(P_{\text{E}\text{CO}_2}\) of 7 kPa had reached a steady-state. The mean value of 10 consecutive breaths was calculated and used in the data analysis. The ventilatory frequency was recorded and the minute ventilation calculated. Generally no more than 7 min were needed before a measurement at steady-state was obtained. In between respiratory measurements the subjects had the mask removed and analgesia testing was performed.

**Data analysis**

Data analysis was performed on the absolute respiration and pain tolerance values and on the values relative to baseline (i.e. the change in minute ventilation and the change in 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 ANOVA 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 which 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 $P_{\text{ETCO}_2}$ of 7 kPa did not differ between the two dose groups: 24.2 (SD 2.3) litre min$^{-1}$ in the 0.2 mg vs 23.5 (1.9) litre min$^{-1}$ in the buprenorphine 0.4 mg group. After infusion of the drug ventilation showed a rapid decline and reached peak depression between $t=150$ and 180 min (Fig. 1). This effect was dose-independent with respect to timing and magnitude. At peak respiratory depression: minute ventilation was 13.1 (1.8) litre min$^{-1}$ (0.2 mg) vs 12.0 (1.3) litre min$^{-1}$ (0.4 mg) (n.s.). The overall effect of buprenorphine on ventilation was dose-independent over the 8 h of the study: 0.2 vs 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 from 0.2 to 0.4 mg buprenorphine. Baseline pain tolerance currents did not differ between the two groups: 16.3 (SD 3.9) mA in the 0.2 mg group vs 15.0 (2.6) mA in the 0.4 mg group (n.s.). At buprenorphine 0.2 mg 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 (Fig. 2). Peak analgesic effect was 29% above baseline current. In contrast, buprenorphine 0.4 mg 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. Peak analgesic effect was 160% above baseline current ($P<0.01$ vs 0.2 mg). The overall effect of buprenorphine on analgesia was dose-dependent over the 8 h of the study (0.2 vs 0.4 mg, $P<0.01$). No sex difference was observed (factors examined sex and sex–dose interaction: $P>0.05$).

Discussion
In the current study we examined the effect of buprenorphine 0.2 and 0.4 mg i.v. (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 to 23.8 mA). In contrast, the timing and magnitude of respiratory depression remained unchanged by doubling the buprenorphine dose (cf. Figs 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 need to be viewed against the background of a more extensive dose–response relationship. This is important taking into account the observation, in some animal studies, of a bell-shaped (inverse U-shaped) dose–response relationship for buprenorphine’s analgesic effects.$^{89}$ In a previous study we assessed the effect of buprenorphine 0.05, 0.1, 0.3...
and 0.6 mg on breathing in a similar study population. We observed a ceiling effect for peak respiratory depression of the drug at doses of greater than 0.1 mg. Although the design of the previous and current studies differs with respect to the duration of measurements (in contrast with the current study, we previously measured breathing continuously for 90 min) we were able to combine these two data sets on peak respiratory depression (Fig. 3). The continuous line in Figure 3 is the data fit using a sigmoid E-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 buprenorphine 0.3 and 0.6 mg data are 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 human beings is not available in the literature. We recently assessed the analgesic effect of i.v. buprenorphine 0.05, 0.1 and 0.3 mg over time in 15 healthy young volunteers using our electrical pain model (A.D., unpublished observation). In Figure 4 we plotted the mean increase in current to achieve pain tolerance (relative to baseline pain tolerance current) vs 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 (0.05–0.6 mg) without causing any ceiling in analgesic effect. 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.

**Differential effect of buprenorphine on analgesia and respiration**

Our data suggest that buprenorphine is a full agonist at MOP receptors involved in pain processing but a partial agonist at MOP receptors involved in respiratory depression. Partial agonism indicates a partial effect despite full MOP-receptor 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). 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. 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 and colleagues showed in rats that progressive MOP-receptor knockdown (i.e. the reduction in

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**Fig 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-max model (continuous line) and a decaying exponential model (broken line) were fitted to the data. Both model fits indicate that the buprenorphine 0.3 and 0.6 mg data are on the flat part of the dose–response relationship.

**Fig 4** Human buprenorphine dose–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. 0.0 mg per 70 kg = placebo (0.9% NaCl). Open symbols: data from ref. 4; closed symbols: data from the current study. To guide the eye a power model was fitted to the data.
MOP-binding sites) with the irreversible MOP-receptor antagonist β-funaltrexamine, caused a marked decrease in alfentanil efficacy. Alfentanil transformed from a full MOP agonist into a partial agonist at reduced MOP availability. It may then be argued that MOP density is greater at pathways in the central nervous system concerned with processing pain than at the respiratory centres in the brainstem andpons. Another explanation for buprenorphine’s behaviour 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.\textsuperscript{11} Raehal and colleagues\textsuperscript{12} showed that genetic disruption of the β-arrestin type 2 (Barr2) gene (Barr2 knockout mice) attenuated the respiratory depression (and acute constipation) caused by morphine. In contrast, morphine-induced antinociception was augmented in the Barr2 knockout mice.\textsuperscript{13} The authors hypothesize that β-arrestin may play an important G-protein independent role in signal transduction via MOP receptors that lead to respiratory depression (and gastrointestinal transit inhibition) but not via MOP receptors that lead to analgesia. G-protein independent but β-arrestin dependent activation has been observed for other receptors of the seven-transmembrane receptor superfamly, such as the β2-adrenergic receptor.\textsuperscript{14} Following the reasoning of Raehal and colleagues\textsuperscript{12} and taking into account our data, this suggests that MOP-receptor 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 MOP-receptor responses, while others (such as buprenorphine) activate the β-arrestin protein with diminished responses. We hypothesize that signal transduction attributable to buprenorphine-activation of MOP receptors 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).\textsuperscript{15} A shared difference in the structure of M6G and buprenorphine with morphine is the modification of the hydroxy group at position C6 of the morphine molecule (morphine: C6–OH, buprenorphine: C6–O–CH\textsubscript{3} and M6G: C6–glucuronide). Possibly this modification at C6 may be the cause for reduced effect at MOP receptors expressed on respiratory neurons (cf. ref. 16). Further studies are needed to clarify this important issue.

In contrast with our previous study,\textsuperscript{4} here we address the issue of buprenorphine’s respiratory safety in the light of its analgesic properties. Opioid-induced respiratory depression is related to over-dosing, 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 led to several warnings related to the use of fentanyl patches for treatment of chronic pain.\textsuperscript{17–20} 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 as buprenorphine’s respiratory effects are limited, buprenorphine has an advantage over other opioids such as fentanyl and morphine which do not show ceiling at a high dose but eventually cause breathing instability and apnoea. However, whether this advantage persists under specific conditions such as old age, (lun)ge disease and ingestion of co-medication needs further study. In opioid-addicts acute co-administration of buprenorphine and benzodiazepines is sometimes associated with fatal respiratory depression.\textsuperscript{21}

**Critique of methods**

We used our pain model as a pharmacological tool and did not intend to simulate clinical (acute or chronic) pain. We had used the acute pain model (electrical transcutaneous stimulation of the skin) previously to successfully study the antinociceptive effects of morphine and M6G.\textsuperscript{7,22} 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. As the healthy volunteers tested in our studies were without pain or inflammation, the term antinociception seems a more appropriate description of the opioid behaviour 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.

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-, hypoventilatory responses, or both, as a result of activation of behavioural respiratory drives;\textsuperscript{23} and hypercapnia has been shown to influence pain testing.\textsuperscript{24} We tried to minimize the complex interactive effects of pain testing and respiratory measurements by allowing ample time between measurements, but we cannot exclude some 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. Post-hoc power analysis indicated that 20 subjects (10 men/10 women) were needed to reveal a sex difference in analgesia after buprenorphine 0.4 mg at the P=0.05 level.

In conclusion, we tested two incremental i.v. 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 none in analgesic effect over a dose range from 0.05 to 0.6 mg.

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