Comparison of the respiratory effects of intravenous buprenorphine and fentanyl in humans and rats

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Background. There is evidence from animal studies suggesting the existence of a ceiling effect for buprenorphine-induced respiratory depression. To study whether an apparent ceiling effect exists for respiratory depression induced by buprenorphine, we compared the respiratory effects of buprenorphine and fentanyl in humans and rats.

Methods. In healthy volunteers, the opioids were infused i.v. over 90 s and measurements of minute ventilation at a fixed end-tidal P\textsubscript{CO\textsubscript{2}} of 7 kPa were obtained for 7 h. Buprenorphine doses were 0.7, 1.4, 4.3 and 8.6 μg kg\textsuperscript{-1} (n=20 subjects) and fentanyl doses 1.1, 2.1, 2.9, 4.3 and 7.1 μg kg\textsuperscript{-1} (n=21). Seven subjects received placebo. In rats, both opioids were infused i.v. over 20 min, and arterial P\textsubscript{CO\textsubscript{2}} was measured 5, 10, 15 and 20 min after the start of fentanyl infusion and 30, 150, 270 and 390 min after the start of buprenorphine infusion. Doses tested were buprenorphine 0, 100, 300, 1000 and 3000 μg kg\textsuperscript{-1} and fentanyl 0, 50, 68 and 90 μg kg\textsuperscript{-1}.

Results. In humans, fentanyl produced a dose-dependent depression of minute ventilation with apnoea at doses ≥2.9 μg kg\textsuperscript{-1}; buprenorphine caused depression of minute ventilation which levelled off at doses ≥3.0 μg kg\textsuperscript{-1} to about 50% of baseline. In rats, the relationship of arterial P\textsubscript{CO\textsubscript{2}} and fentanyl dose was linear, with maximum respiratory depression at 20 min (maximum P\textsubscript{aCO\textsubscript{2}} 8.0 kPa). Irrespective of the time at which measurements were obtained, buprenorphine showed a non-linear effect on P\textsubscript{aCO\textsubscript{2}}, with a ceiling effect at doses ≥1.4 μg kg\textsuperscript{-1}. The effect on P\textsubscript{aCO\textsubscript{2}} was modest (maximum value measured, 5.5 kPa).

Conclusions. Our data confirm a ceiling effect of buprenorphine but not fentanyl with respect to respiratory depression.

Keywords: analgesics, opioid; complications, opioid-induced respiratory depression; complications, respiratory depression; receptors, \(\mu\)-opioid; ventilation, analgesics, effects of respiration

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Buprenorphine is a semisynthetic opioid analgesic used in clinical practice since 1979.\textsuperscript{1} Recently, interest in buprenorphine has been renewed because of the introduction of a new transdermal formulation for the treatment of chronic pain and the use of buprenorphine in the treatment of heroin addiction.\textsuperscript{1–3} Buprenorphine is a potent analgesic with agonistic activity at the \(\mu\)-opioid receptor and the opioid receptor-like 1 (ORL\textsubscript{1}) receptor, and antagonistic properties at the \(\kappa\)-opioid receptor.\textsuperscript{4,5} In humans, buprenorphine behaves as a typical \(\mu\)-opioid receptor agonist, showing analgesia, sedation, nausea, delayed gastric emptying and respiratory depression.\textsuperscript{4,6} Animal studies suggest that buprenorphine, in contrast to other opioids, shows a ceiling in its \(\mu\)-agonist behaviour, such as analgesia and respiratory depression.\textsuperscript{4,7–9} A ceiling is best defined as an apparent maximum effect regardless of drug dose. This is an important observation which has been poorly studied in humans.
In this study we assessed whether there is an apparent maximum in opioid-induced respiratory depression for buprenorphine. We measured the respiratory responses to buprenorphine and compared them with responses to fentanyl, a μ-opioid receptor agonist for which no ceiling has been observed.

**Methods**

**Human studies**

Forty-eight volunteers (24 men, 24 women) participated in the study after approval had been obtained from the local human ethics committee. All subjects were healthy and did not have a history of illicit substance abuse. They were asked to refrain from stimulants and depressant substances for at least 12 h before the study. Each subject participated once.

To study ventilation we used the dynamic end-tidal forcing technique. This technique enables the investigator to force end-tidal $\text{PCO}_2$ ($\text{PETCO}_2$) and end-tidal $\text{PO}_2$ ($\text{PETO}_2$) to follow a specific pattern in time. We clamped the $\text{PETCO}_2$ and $\text{PETO}_2$ 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 the nose and mouth (a noseclip 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 running ACQ software (Erik Kruyt, Leiden University Medical Center, Leiden, The Netherlands) provided control signals to the mass flow controllers, allowing 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 ($\text{SpO}_2$) of arterial haemoglobin with a finger probe. All relevant variables (minute ventilation, $\text{SpO}_2$, $\text{PETCO}_2$, and $\text{PETO}_2$) were available for on-line analysis (using RRDP software; Erik Olofsen, Leiden University Medical Center) and stored on a breath-to-breath basis for further analysis. The Bispectral Index (BIS®) of the EEG was monitored with a BIS XP machine (Aspect Medical Systems, Newton, MA, USA; release 2002) using a four-lead electrode placed on the forehead as specified by the manufacturer. BIS values were collected at 1-min intervals.

The study was double-blind, randomized and placebo-controlled. Before testing, all subjects received ondansetron 4 mg i.v. The subjects were randomly assigned to receive placebo (NaCl 0.9%), buprenorphine (Reckitt Benckiser Healthcare, Hull, UK) or fentanyl (Janssen-Cilag, Tilburg, The Netherlands). The following doses were given: placebo, 9 ml ($n=7$); buprenorphine in 9 ml saline, 0.7 μg kg$^{-1}$ ($n=5$), 1.4 μg kg$^{-1}$ ($n=5$), 4.3 μg kg$^{-1}$ ($n=5$) and 8.6 μg kg$^{-1}$ ($n=5$); fentanyl in 9 ml saline, 1.1 μg kg$^{-1}$ ($n=5$), 2.2 μg kg$^{-1}$ ($n=5$), 2.9 μg kg$^{-1}$ ($n=5$), 4.3 μg kg$^{-1}$ ($n=5$) and 7.1 μg kg$^{-1}$ ($n=1$). The highest fentanyl dose (7.1 μg kg$^{-1}$) was tested only once. After the first subject had been given this dose, the respiratory effects were so severe (apnoea >5 min, and $\text{SpO}_2$ dropped below 70%) that the blinding of this experiment was broken and a decision was made to no longer infuse the highest fentanyl dose. The data of the single subject receiving 7.1 μg kg$^{-1}$ were used in the analysis.

The respiratory studies started after a period of acclimatization to the apparatus and ventilation (at a $\text{PETCO}_2$ of 7 kPa) had reached steady state. Next the drug was infused slowly over 90 s. Subsequently, continuous respiratory measurements were obtained for 80–90 min, followed by 5–10 min measurements at 30-min intervals (until 4 h after drug infusion) and then at 60-min intervals. If ventilation returned to baseline values (defined by at least 5 min at or above baseline) before the end of the measurement period, the study was ended. If this did not happen or there was no systematic respiratory depressant effect, the study ended 7 h after drug infusion.

**Data analysis**

We performed a 1-min average on the ventilation data of individual subjects. From these data we calculated peak ventilatory depression, time to peak effect and time to end of effect (i.e. return to baseline). The dose–peak ventilatory depression data were analysed using the following sigmoid $E_{\text{max}}$ model:

\[
\text{Effect(dose)} = E_{\text{max}} - (E_{\text{max}} - E_{\text{min}}) \cdot \left( \frac{\{\text{dose/ED}_{50}\}^{\gamma}}{1 + (\text{dose/ED}_{50})^{\gamma}} \right)
\]

where dose is the drug dose applied, $\text{ED}_{50}$ the estimated dose causing 50% effect, data analysis $E_{\text{max}}$ and $E_{\text{min}}$ the maximum and minimum of the sigmoid function, and $\gamma$ a shape parameter. The model parameters were estimated using non-linear regression analysis (Nonmem version V, level 1.1; a data analysis program for non-linear mixed effects modelling). The likelihood ratio criterion was used to assess whether $E_{\text{min}}$ differed significantly from 0.

In order to get an impression of the average drug effect on respiration over the measurement time, we assessed the area between the curves standardized by the length of the study. The curves that are involved are those for measured ventilatory depression data and for on-drug baseline (which by definition equals 1; see also Fig. 1). An average drug effect of 40 indicates an average of 40% respiratory depression over the measured time period (i.e. from time of drug infusion to end of effect or end of study if time to end of effect had not been reached within 420 min).
The average age of the subjects was 22 yr (range 19–34 yr). Mean weight and height of the subjects was 72 kg (range 53–93 kg) and 176 cm (range 160–192 cm), respectively.

**Placebo**

Placebo had no systematic effect on ventilation over the 420-min measurement period. Predrug ventilation was 22.7 (6.1) litre min⁻¹. The lowest ventilation after drug administration of the opioid or vehicle while the cannula was in the right jugular vein. The cannula in the right jugular vein was used for administration of the opioid or vehicle while the cannula in the left femoral artery was used for collection of arterial blood samples. The cannulae are made from pyrogen-free, non-sterile polyethylene tubing. The cannulae were tunnelled subcutaneously and fixed at the back of the neck with a rubber ring. In order to prevent clotting and cannula obstruction the cannulae were filled with a 25% (w/v) polyvinylpyrrolidone solution (PVP; Brocacef, Maarsen, The Netherlands) in pyrogen-free physiological saline (B. Braun Melsungen, Melsungen, Germany) containing heparin 20 IU/ml.

**Drugs and dosages**

Fentanyl was dissolved in saline; buprenorphine was dissolved in saline with the aid of two drops of polysorbate 80 (Hospital Pharmacy, Leiden University Medical Center). Henceforth, the doses of buprenorphine and fentanyl are expressed as free base.

Each animal was tested once. For buprenorphine the following doses were tested: 0 (vehicle), 100, 300, 1000 and 3000 µg kg⁻¹. For fentanyl the doses were 0 (vehicle), 50, 68 and 90 µg kg⁻¹. Fentanyl and buprenorphine were infused i.v. over 20 min by constant-rate infusion using an infusion pump (BAS Bioanalytical Systems, West Lafayette, IN, USA). Animals were randomly assigned to the treatment groups with seven animals in each treatment level.

**Measurement of arterial PCO2**

Arterial blood samples were obtained at fixed times for measurement of $P_{aCO_2}$ using a Bayer 278 Blood gas analyser (Bayer, Mijdrecht, The Netherlands). For buprenorphine these times were: baseline (5–10 min before drug infusion), 0, 30, 60, 120, 270 and 390 min after drug administration. For fentanyl the times were: baseline, 5, 10, 15 and 20 min after drug administration. Each blood sample withdrawn was replaced by an equal volume of heparinized saline 0.9% (20 IU heparin/ml). The difference in sampling schedule is related to the difference in speed of onset of the two tested opioids, with immediate changes in $P_{aCO_2}$ observed after fentanyl but not after buprenorphine infusion. During the experiments body temperature was maintained at 37.5°C with a CMA/150 Temperature Controller (BAS Bioanalytical Systems).

**Statistical analysis**

The buprenorphine and fentanyl studies were analysed separately. One-way analysis of variance was performed to assess the effect of drug dose for each time point, with post hoc Bonferroni correction for multiple comparisons. $P$-values $<0.05$ were considered significant.

**Results**

**Human studies**

The average age of the subjects was 22 yr (range 19–34 yr). Mean weight and height of the subjects was 72 kg (range 53–93 kg) and 176 cm (range 160–192 cm), respectively.

**Placebo**

Placebo had no systematic effect on ventilation over the 420-min measurement period. Predrug ventilation was 22.7 (6.1) litre min⁻¹. The lowest ventilation after drug...
Infusion was at 180 min: 19.6 (4.6) litre min⁻¹. The mean average drug effect was 0.1 (0.1).

**Fentanyl and buprenorphine time profiles**

The individual ventilatory responses of the subjects are given in Figures 2 and 3. For both drugs, predrug ventilation did not differ among the doses: fentanyl 24.1 (6.0) litre min⁻¹, buprenorphine 24.5 (4.1) litre min⁻¹. After fentanyl, four subjects developed a period of apnoea shortly after the infusion, one after 2.9 μg kg⁻¹ (duration <3 min, lowest SpO₂ measured 92%), two after 4.3 μg kg⁻¹ (duration <3 min, lowest SpO₂ measured 91 and 93%) and one after 7.1 μg kg⁻¹ (8 min). Time to fentanyl peak effect did not differ among the doses tested: 4.8 (2.2) min. After buprenorphine, none of the subjects receiving buprenorphine developed apnoea. Time to buprenorphine peak effect was dose-independent and averaged 117 (58) min.

**Peak drug effect and average drug effect**

The dose–peak effect relationships are given in Figure 4. For fentanyl there was a steep dose–response relationship, eventually reaching apnoea. The data fit yielded the following parameter values: Eₘₐₓ 20.1 (2.9) litre min⁻¹, E₅₀ 1.5 (0.5) μg and γ 2.0 (1.4); Eₘᵢₙ did not differ significantly from 0. For buprenorphine the dose–peak effect relationship showed an initial steep decrease in ventilation which levelled off at doses >2 μg kg⁻¹. The data fit yielded the following parameter values: Eₘₐₓ 20.0 (0.8) litre min⁻¹, E₅₀ 0.9 (0.1) μg and γ 3.0 (0.9); Eₘᵢₙ differed significantly from 0 and was estimated at 9.1 (0.6) litre min⁻¹. The Eₘᵢₙ value indicates that, at a background of 7 kPa end-tidal Pₐₖ, the lowest value of minute ventilation after buprenorphine is 9 litres min⁻¹.

The dose–average drug effect relationships are shown in Figure 5. For fentanyl there was a steep dose–effect relationship, with increasing values at increasing fentanyl doses (P<0.001). In contrast, for buprenorphine the average drug effect did not differ among doses.

**Side-effects**

The one subject dosed with fentanyl 7.1 μg kg⁻¹ developed apnoea within 4 min of infusion with a drop in SpO₂ to 68%. She was instructed to take regular breaths and 100% inspired oxygen was given. This resulted in a quick return to SpO₂ values >90%. The apnoic episode lasted about 8 min, after which breathing resumed with Pₐₖ values >7 kPa. We did not remove the ventilation data points at a higher Pₐₖ level than targeted in the study. One subject receiving buprenorphine 8.6 μg kg⁻¹ developed severe nausea about 60 min after the infusion of the drug. During this period of nausea (lasting about 30 min) he had a hyperventilatory response. Time to end of effect was set at 420 min. We decided to leave the data as they were as this did not affect the data on peak effect and time to peak effect. However, it did cause...
underestimation of the average drug effect of this subject.

All other side-effects were mild, ranging from nausea to sedation. Sedation developed in most subjects after they had received an opioid, but was marked after buprenorphine 8.6 μg kg⁻¹. BIS values were >90 during respiratory measurements in all subjects, irrespective of the opioid dose. Decreases in BIS occurred between respiratory measurements and were always related to the occurrence of sleep.

Fig 3 Individual ventilatory responses after infusion of buprenorphine: (A) 0.7; (B) 1.4; (C) 4.3; and (D) 8.6 μg kg⁻¹. Ventilation is normalized relative to baseline values. Different symbols and lines depict different subjects.

Fig 4 Dose–response relationships for (A) fentanyl and (B) buprenorphine. The response is the peak ventilatory depression. The line through the data is the fit to the Hill equation. 0 μg kg⁻¹ is placebo. Data are mean (SD).
Rat studies

The effects of both opioids on $P_{aCO_2}$ are shown in Figures 6 and 7. As predicted, the increase in $P_{aCO_2}$ after the infusion of fentanyl was rapid, with significant effects apparent just 5 min after the initiation of the fentanyl infusion.

After fentanyl, a significant dose–effect was observed at times $t=5$, 10 and 15 min ($P<0.01$), with an almost linear
dose–response relationship (Fig. 5). At \( t = 20 \) min, a maximum in respiratory depression (\( P_{\text{aCO}_2} 7.5 \) kPa) was observed at all doses tested (fentanyl vs vehicle, \( P < 0.001 \); no significant differences among the fentanyl doses). The changes in \( P_{\text{aCO}_2} \) dissipated rapidly after the termination of the fentanyl infusion.

Irrespective of the time at which measurements were obtained and dose, buprenorphine showed a relatively small increase in \( P_{\text{aCO}_2} \) of 1–1.5 kPa (buprenorphine vs vehicle, \( P < 0.05 \); no significant differences among the buprenorphine doses were observed). This indicates that a plateau in respiratory depression occurred at a dose of buprenorphine 0.1 mg kg\(^{-1}\), causing an increase in \( P_{\text{aCO}_2} \) of about 50% of the maximum increase in \( P_{\text{aCO}_2} \) observed after fentanyl.

**Discussion**

In humans and rats, we studied two potent opioids, buprenorphine and fentanyl, and observed distinct differences in their respiratory behaviour. The data obtained in both species were similar. In contrast to fentanyl, buprenorphine showed a ceiling (or apparent maximum) effect in its ability to cause respiratory depression.

The end-tidal CO\(_2\) was controlled within 0.1 kPa (mean SD of \( P_{\text{eCO}_2} \) fluctuations). In some cases, deviations from target \( P_{\text{eCO}_2} \) greater than 0.4 kPa did occur related to the short periods of relative hyperventilation following apnoea (Fig. 2). While these deviations from target \( P_{\text{eCO}_2} \) may have influenced the time profile of individual curves and underestimated the average drug effect, we do not believe that the final conclusions of the study were influenced significantly. In instances when apnoea did occur, we coached the subjects to take deep breaths. Coaching may have activated behavioural control of breathing and consequently may have influenced the study results (average drug effect).\(^{13}\) However, the influence of 3–8 min of coaching during apnoea on a 7-h experiment was minimal.

We were able to successfully coach the subjects through the episode of apnoea after fentanyl 2.9 and 4.3 \( \mu \)g kg\(^{-1}\). However, we felt that the prolonged period of apnoea with low \( S_{\text{PO}_2} \) observed in the first subject dosed with fentanyl 7.1 \( \mu \)g kg\(^{-1}\) was unacceptable and so we decided to restrict our study to a maximum fentanyl dose of 4.3 \( \mu \)g kg\(^{-1}\). Similarly, in rats, we had observed in a pilot study that short-term infusions of fentanyl but not buprenorphine caused the death of several of our animals. To overcome this problem, we infused both tested drugs over 20 min in the rats. The different method of drug administration between humans and rats resulted in evident differences in plasma drug–time profiles.

In the human study we focused our data analysis on two measures of respiratory outcome: peak effect and the
average drug effect. Average drug effect divided by the duration of effect is considered a weighted average of a response\textsuperscript{12} and allows comparisons among drug doses when no pharmacokinetic data are available. Although both measures (peak effect and average drug effect) are related to the pharmacokinetics and pharmacodynamics of the infused drug, they represent two distinct features of the drug which complement each other. Peak effect is related to the rise in opioid concentration in the brain compartment, subsequent attachment to the opioid receptor and neuronal dynamics. The average drug effect is related to the accumulation of the drug within the brain compartment, receptor kinetics (association and, more importantly, dissociation) and neuronal dynamics and gives an indication of the opioid’s respiratory efficacy. Both indices showed great variability (see the standard deviations in Figs 4 and 5). The early effects were especially variable, which may be due to variability in the central volume of distribution, transit and uptake of the drug in the lungs (fentanyl)\textsuperscript{14} and passage across the blood–brain barrier.

In humans, the relationships between buprenorphine dose and peak effect and average drug effect were non-linear. These findings are in contrast with the observations that the relationships of peak effect and average drug effect and dose of fentanyl were linear over the dose range from 0 to 4.3 \( \mu \text{g kg}^{-1} \). We remain unimpressed on the effect of fentanyl at doses > 4.3 \( \mu \text{g kg}^{-1} \), with only data from one subject at 7.1 \( \mu \text{g kg}^{-1} \). However, when we take into account the data from this one subject together with the animal data, it is evident that also at the higher fentanyl doses the human dose–response curve will have linear characteristics. Few studies have systematically addressed the issue of buprenorphine-induced respiratory depression in humans. Comparison of our data with these studies is difficult. In our studies we used isocapnia (constant end-tidal \( P_{\text{CO}_2} \)) and measured ventilation. Other studies used either no control for carbon dioxide, a constant inspired carbon dioxide concentration or less informative measures, such as respiratory rate. In two studies, Walsh and colleagues assessed the effect of buprenorphine 0.5–32 mg sublingually on respiratory rate and oxygen saturation.\textsuperscript{15,16} They observed a non-linear dose–response curve with a plateau arising between 0.4 and 0.8 mg. Despite the fact that neither respiratory rate nor oxygen saturation is a valid marker of respiration, the results of the studies of Walsh and colleagues do give a qualitative suggestion of buprenorphine’s behaviour in humans. Our data, obtained at isocapnia, give a quantitative indication of the occurrence of a ceiling in buprenorphine-induced respiratory depression at i.v. doses of \( \geq 2.9 \mu \text{g kg}^{-1} \).

Despite the overt differences in methodology between the human and animal studies, the results of the studies were similar. In the animal studies, we used arterial \( P_{\text{CO}_2} \) as a surrogate measure of minute ventilation. The measured \( P_{\text{acO}_2} \) in our studies is not only determined by the respiratory depression \textit{per se}, but also by its complex interaction with ventilation. The increase in \( P_{\text{acO}_2} \) has a drug-dependent stimulatory effect on breathing causing the (drug-dependent) elimination of carbon dioxide from the lung. We may therefore have underestimated any respiratory depression observed in the animals. An example of the underestimation of respiratory depression in human studies performed under poikilocapnic conditions (i.e. end-tidal \( P_{\text{CO}_2} \) not kept constant) is the observation by Mildh and colleagues of a very high \( EC_{50} \) value (drug concentration causing 50% effect) for fentanyl-induced respiratory depression (6.1 ng ml\(^{-1}\)).\textsuperscript{10} In that study ventilation was measured and fentanyl was infused slowly, allowing the accumulation of carbon dioxide, which prevented the occurrence of severe respiratory depression and apnoea. Bouillon and colleagues addressed this issue by using indirect–response models to calculate the \( EC_{50} \) and taking into account both drug and carbon dioxide effects.\textsuperscript{17} Although calculation of the \( EC_{50} \) is not directly possible from our study, using pharmacokinetic data from the literature we were able to estimate a value of 1.5 ng ml\(^{-1}\), which is a factor of 4 smaller than the value obtained by Mildh and colleagues.

Considering all of the above, we do not believe that our animal data lack importance. Like the studies of Walsh and colleagues, these data give qualitative proof of the behaviour of both opioids. In humans, the occurrence of apnoea shortly after the 90-s infusion of high-dose fentanyl (200 \( \mu \text{g} \) or greater) is related to the rapid increase in blood fentanyl concentration, its rapid passage across the blood–brain barrier (the fentanyl blood–effect site equilibration half-life is about 5 min),\textsuperscript{18} with consequently high brain concentrations and almost immediate attachment to the \( \mu \)-receptor. This caused rapid depression of respiratory neurons expressing the \( \mu \)-opioid receptor (peak respiratory effect after fentanyl occurred at 4.8 min). Buprenorphine, like fentanyl, is highly lipophilic and shows relatively rapid passage across the blood–brain barrier. However, in contrast to fentanyl, buprenorphine displays slow opioid-receptor association and dissociation kinetics.\textsuperscript{19} This may have prevented rapid changes in ventilation in our population despite relatively high brain concentrations (peak respiratory effect after buprenorphine occurred at 117 min).

It is generally believed that both fentanyl and buprenorphine produce their intended effect (analgesia) via an action at the \( \mu \)-opioid receptor gene (\textit{OPRM1}). Using exon 2 \textit{Oprm} knockout mice, we observed that the \( \mu \)-opioid receptor is the source of morphine-induced antinociception and respiratory depression.\textsuperscript{20,21} Involvement of other opioid receptors (\( \kappa \), \( \delta \) - or ORL\textsubscript{1}-receptors) in morphine-induced respiratory depression seems unlikely. We believe this also holds true for other opioids, such as fentanyl. Hence, we postulate that the effect of fentanyl at the \( \mu \)-opioid receptor is exclusively responsible for the (almost-linear) dose–response relationship found in our volunteers and animals (Figs 3–5). In rats, the finding of a maximum effect of fentanyl 20 min after the start of the infusion shows the maximum effect on respiration that is possible in living animals (fentanyl doses >90 \( \mu \text{g kg}^{-1} \) are fatal). Our human
(average drug effect, Fig. 4) and animal data indicate that fentanyl is a full agonist at the μ-opioid receptor, with high intrinsic activity. The non-linear buprenorphine dose–response relationship we observed is in agreement with earlier human and animal studies on its respiratory effect. 7–9 Especially in rats, data show a ceiling in buprenorphine-induced respiratory depression at doses above 0.1 mg kg \(^{-1}\). 1,7,8 In rhesus monkeys a similar observation was made for doses greater than 1.0 mg kg \(^{-1}\). 9 This latter study is of interest since it measured steady-state minute ventilation at a fixed inspired carbon dioxide concentration of 5%. Partial agonism of buprenorphine at the μ-opioid receptor is generally held responsible for the ceiling phenomenon. 47 Partial agonism indicates a partial (respiratory) effect despite full μ-receptor occupancy. Recently, Lutty and colleagues proposed a different mechanism for the non-linear dose–response. 7 They showed that buprenorphine (but not morphine) given to mice activates ORL \(_1\)-receptors, compromising antinoicetion mediated via μ-opioid receptors. Extrapolation of these animal data on antinoiception to our respiratory studies would suggest that buprenorphine’s action at the ORL \(_1\)-receptor would cause the reduction of respiratory depression from buprenorphine’s action at the μ-receptor. In this respect buprenorphine would act as a respiratory stimulant at the ORL \(_1\)-receptor. Just one study has addressed the influence of the ORL \(_1\)-receptor on respiration. 22 In an in vitro preparation of the newborn rat brainstem, activation of the ORL \(_1\)-receptor produced depression of the generation of respiratory rhythm. This observation does not support the hypothesis of involvement of the ORL \(_1\)-receptor in the development of a ceiling in buprenorphine’s respiratory effect. The current data are very scanty and further studies are required to elucidate the involvement of the ORL \(_1\)-receptor in opioid-induced respiratory depression.

The observation of a ceiling in buprenorphine-induced respiratory depression has contributed to the notion that buprenorphine’s respiratory effects are limited. 1 (Significant or fatal respiratory depression has only been reported for buprenorphine combined with sedative drugs, such as benzodiazepines). 23 However, buprenorphine’s safety profile should be considered against the background of its analgesic profile. For example, if a ceiling in respiratory depression coincided with ceiling in analgesia, then the value of buprenorphine would be limited in clinical practice. While there is evidence from animal data of the occurrence of a ceiling or even a bell-shaped response curve in the analgesic effect of buprenorphine (at doses >1.0 mg kg \(^{-1}\)), 5,7,24 there are no good (placebo-controlled, randomized) human studies available. Our data and those of others obtained in rodents indicate that the ceiling in respiratory effect occurs at a much lower dose (0.1 mg kg \(^{-1}\)) than the ceiling in analgesic effect (1.0 mg kg \(^{-1}\)), which indicates the relative safety of buprenorphine combined with its ability to produce effective analgesia in these animals. 5,7,9,24 Before we can extrapolate these claims to humans, we need good clinical studies to determine whether there is a ceiling for analgesia and to assess the dose at which it occurs. Our study cannot address the issue of buprenorphine’s efficacy and safety in the light of its analgesic properties.

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**References**


