



Universiteit
Leiden
The Netherlands

Reversal of drug-affected breathing

Bijl, J.H.L.

Citation

Bijl, J. H. L. (2006, June 21). *Reversal of drug-affected breathing*. Retrieved from <https://hdl.handle.net/1887/4419>

Version: Corrected Publisher's Version

License: [Licence agreement concerning inclusion of doctoral thesis in the Institutional Repository of the University of Leiden](#)

Downloaded from: <https://hdl.handle.net/1887/4419>

Note: To cite this publication please use the final published version (if applicable).

4 Naloxone-Reversal of Opioid-Induced Respiratory Depression with Special Emphasis on Buprenorphine

Long-acting opioids are important tools in the treatment of postoperative acute pain and chronic cancer and non-cancer pain. When selecting one of the available compounds, not only the analgesic properties but also the safety profile of the drug needs to be considered. In general, opioids are well tolerated. Among the opioid-typical side effects, however, respiratory depression is of special importance because of the risk of fatal outcome for the patient.

Buprenorphine is a potent analgesic (100 times more potent than morphine) with μ -agonistic, ORL₁-agonistic and κ -antagonistic opioid properties.¹ In patients, buprenorphine is used for treatment of acute and chronic pain *via* various administration modes, such as intravenous (i.v.), transdermal, sublingual, epidural or spinal administration. In humans, buprenorphine behaves as a typical μ -opioid receptor agonist showing analgesia, euphoria, sedation, respiratory depression and pupillary constriction.^{1,2} Buprenorphine has high affinity for opioid receptors and slow receptor association and dissociation kinetics as compared to other opioids.³ After an intravenous infusion of 0.2–0.4 mg/70 kg the duration of action of buprenorphine is about 6 to 8 hours. Data obtained in opioid-naïve volunteers indicate that buprenorphine causes dose-dependent respiratory depression which levels off at greater buprenorphine doses (*i.e.*, plateau or ceiling in respiratory effect).⁴

Surprisingly few studies have addressed the ability to reverse the respiratory effects of opioids in general and buprenorphine in specific. Just two studies from the literature published in the 1980's as well as some anecdotal data suggest that the respiratory depression from buprenorphine is resistant to antagonism by naloxone.⁵⁻⁷ While relatively low bolus doses of intravenous naloxone had no effect, high doses (2.5 to 10 mg) caused only partial reversal of buprenorphine's respiratory effects. These results may be explained by the short duration of action of a bolus dose of naloxone resulting from a rapid elimination combined with the high affinity of buprenorphine for μ -opioid receptors. Consequently, a bolus dose of naloxone may be unable to displace buprenorphine from the opioid receptors. The buprenorphine/naloxone data contrast data on the ability to reverse fentanyl-induced respiratory depression, which is considered relatively easy. Short naloxone infusions up to 0.4 mg cause full reversal of fentanyl-induced respiratory depression in patients during halothane/nitrous oxide anesthesia.⁸

We performed a series of experiments to study the influence of naloxone on buprenorphine-induced respiratory depression. Our aim was to obtain a naloxone-dosing regimen that would

cause full reversal of buprenorphine-induced respiratory depression. Initially (Study 1) we assessed the effect of 0.8 mg naloxone (or placebo) on 0.2 mg i.v. buprenorphine-induced respiratory depression in healthy volunteers. In a subsequent study (Study 2) we explored which naloxone dose causes full reversal of 0.2 mg i.v. buprenorphine-induced respiratory depression. In order to do so we tested various naloxone doses in the range from 0.5 to 7 mg in separate subjects. In another study (Study 3) we assessed the effect of a continuous naloxone (or placebo) infusion on 0.2 and 0.4 mg i.v. buprenorphine-induced respiratory depression. Finally, in order to compare the results of studies 1–3 we assessed the effect of just 400 μg naloxone (or placebo) on 0.15 $\text{mg}\cdot\text{kg}^{-1}$ i.v. morphine-induced respiratory depression (Study 4) and 4 $\mu\text{g}\cdot\text{kg}^{-1}$ naloxone on alfentanil-induced depression of the ventilatory response to hypoxia (Study 5). We hypothesized that while 300–400 μg naloxone was sufficient to fully reverse morphine- and alfentanil-induced respiratory depression, much greater doses and a continuous infusion are needed to reverse buprenorphine-induced respiratory depression.

Methods

A total of ninety-nine male and female subjects (age range 20–30 years, weight 54–93 kg) participated in the studies after approval of the protocols was obtained from the local Human Ethics Committee. We obtained oral and written consent. All subjects were healthy and did not have a history of illicit drug use or mental disease. All women were taking oral contraceptives. Subjects were asked to have a normal night of sleep and not to eat or drink for at least 6 h prior to the study. They were comfortably seated in a hospital bed for the duration of the study.

Respiration

In- and expired gas flows were measured with a pneumotachograph (Hans Rudolph, Wyandotte, MI, USA) connected to a pressure transducer and electronically integrated to yield a volume signal. The volume signal was calibrated with a motor-driven piston pump (stroke volume 1000 ml, at a frequency of $20\cdot\text{min}^{-1}$). The pneumotachograph was connected to a T-piece. One arm of the T-piece received a gas mixture with a flow of $45\text{ l}\cdot\text{min}^{-1}$ from a gas mixing system, consisting of three mass flow controllers (Bronkhorst High-Tech BV, Veenendaal, The Netherlands) with which the flow of O_2 , CO_2 and N_2 could be set individually at a desired level. A personal computer provided control signals to the mass flow controllers so that the composition of the inspired gas mixtures could be adjusted to force end-tidal oxygen and carbon dioxide concentrations ($P_{\text{ET}}\text{O}_2$ and $P_{\text{ET}}\text{CO}_2$) to follow a specified pattern in time, independent of the ventilatory response (*i.e.*, dynamic end-tidal forcing).⁹ In the studies 1–4, $P_{\text{ET}}\text{CO}_2$ was clamped at 7.0 kPa throughout the measurements (about 1 kPa above resting values), while $P_{\text{ET}}\text{O}_2$ was maintained at a normoxic value of 14.5 kPa. In study 5, $P_{\text{ET}}\text{CO}_2$ was clamped at 7.0 kPa and $P_{\text{ET}}\text{O}_2$ lowered to 6.0 kPa for 3 min. The O_2 and CO_2 concentrations and the arterial Hb- O_2 saturation (SpO_2) were measured with a gas

monitor near the mouth (Multicap, Datex, Helsinki, Finland) and a pulse oximeter (Masimo, Irvine, CA, USA) using a finger probe, respectively. The gas monitor was calibrated with gas mixtures of known composition delivered by a gas-mixing pump (Wösthoff, Bochum, Germany). $P_{ET}CO_2$, $P_{ET}O_2$, inspired minute ventilation and SpO_2 were collected on a breath-to-breath basis and stored on disc for further analysis.

Study Design and Data Analysis

The studies were placebo-controlled and had a double blind design (except study 5, see below). The local pharmacy delivered the buprenorphine hydrochloride (Reckitt Benckiser Healthcare Ltd, Hull, UK), alfentanil hydrochloride (Janssen-Cilag BV, Tilburg, The Netherlands), morphine hydrochloride and naloxone hydrochloride (both manufactured by the local pharmacy), and placebo (NaCl 0.9%). Randomization and preparation of the syringes was performed by a physician not involved in the study using randomization lists obtained from www.randomization.com. All buprenorphine and naloxone doses are per 70 kg. All bolus infusions were given over 90 s. Each subject participated once in any of the studies. Values are reported as mean \pm SEM, unless otherwise stated.

Study 1

Sixteen subjects participated in this study. All received 0.2 mg buprenorphine i.v. (at time $t = 0$) followed by 800 μ g naloxone i.v. ($n = 8$) or placebo ($n = 8$) at $t = 120$ min. At the following times steady-state ventilation was measured (measurement period 7 min): -10 min (ten min prior to drug infusion), 15, 75, 140, 180, 240, 300, 360, 420 and 480 min after drug infusion. t -Tests were performed to detect a significant effect of naloxone on ventilation at the $P < 0.05$ level.

Study 2

Twenty-four subjects participated in this study. All received 0.1 mg buprenorphine i.v. at $t = 2$ min, followed by a continuous infusion for 1 h of $0.1 \text{ mg}\cdot\text{h}^{-1}$ (total dose = 0.2 mg in 60 min). At $t = 32$ min, x mg naloxone i.v. was given followed by a continuous infusion for 30-min of $2\cdot x\cdot\text{h}^{-1}$ (total dose = $2\cdot x$ mg in 30 min). The following values of $2\cdot x$ were tested: 0 (placebo), 0.5, 1, 2, 3, 4, 5, 6 and 7 mg. Each dose was tested in two subjects, except for placebo that was tested in eight subjects. Breathing was measured continuously from 2 min prior to buprenorphine infusion until 90 min after the start of infusion.

The breath-to-breath data were averaged over 1-min periods. An ensemble average was performed on the data of the eight subjects receiving the buprenorphine/placebo combination, allowing the calculation of buprenorphine/placebo-induced respiratory effect at various times. To quantify the respiratory effect of naloxone relative to placebo we used the following formula on the data of each subject that had received the buprenorphine–naloxone combination:

$$\text{Reversal}(z) = [V_{i, \text{naloxone}}(z) - V_{i, \text{placebo}}(z)] / [V_{i, \text{baseline}} - V_{i, \text{placebo}}(z)]$$

where period z ranges from $t = 61$ to $t = 63$ min (*i.e.*, 1 min before to 1 min after the end of the continuous naloxone infusion); $V_{i, \text{placebo}}(z)$ is mean minute ventilation in the placebo during period z , $V_{i, \text{naloxone}}(z)$ mean ventilation of the equivalent period after naloxone, and $V_{i, \text{baseline}}$ mean ventilation of the 2 min prior to the buprenorphine infusion. This analysis will yield a quantitative measure of reversal with 0 indicating no reversal (naloxone no better than placebo) and 1 full reversal (response returned to pre-buprenorphine level).

In order to get an impression of the naloxone dose-effect relationship on this 0.2 mg buprenorphine-induced respiratory depression, we fitted the dose-reversal data using the following sigmoid E_{max} function incorporating an inhibitory component (using NONMEM):

$$\text{Reversal} = (\text{dose}/D_1)^\gamma / (1 + (\text{dose}/D_1)^\gamma) \cdot [1/(1 + (\text{dose}/D_2)^\gamma)]$$

where D_1 and D_2 are the naloxone doses causing 50% reversal and return to 50% depression, respectively, and γ a shape parameter.

Study 3

Thirty-two subjects participated in this study.

STUDY 3.1: Sixteen received 0.1 mg buprenorphine i.v. at $t = 2$ min, followed by a continuous infusion for 1 h of $0.1 \text{ mg}\cdot\text{h}^{-1}$ (total dose = 0.2 mg in 60 min). At $t = 32$ min, 2 mg naloxone ($n = 8$) or placebo ($n = 8$) was infused, followed by an infusion of $4 \text{ mg}\cdot\text{h}^{-1}$ for 2 h.

STUDY 3.2: Sixteen other subjects received 0.2 mg buprenorphine i.v. at $t = 2$ min, followed by a continuous infusion for 1 h of $0.2 \text{ mg}\cdot\text{h}^{-1}$ (total dose = 0.4 mg in 60 min). At $t = 32$ min, 3 mg naloxone ($n = 8$) or placebo ($n = 8$) was infused, followed by a continuous infusion of $4 \text{ mg}\cdot\text{h}^{-1}$ for 2 h. The bolus naloxone dose was 50% greater than that of Study 3.1. This was based on a pilot study in 3 subjects that showed the need for a greater initial dose of naloxone after 0.4 mg buprenorphine compared to 0.2 mg buprenorphine.

Ventilation was initially measured continuously from 2 min prior to buprenorphine infusion until 120 min after the start of infusion. Subsequently measurements were made at 30-min intervals until $t = 240$ min, after which hourly measurements were performed until $t = 420$ min.

The breath-to-breath data were averaged over 1-min periods. An ensemble average was performed on the naloxone and placebo data groups. The values were compared to baseline ventilation (\pm its 95% confidence interval).¹⁰ When the mean ventilation value equalled or crossed [baseline ventilation – $1 \times 95\%$ confidence interval], we somewhat arbitrarily assumed that ventilation had returned to pre-drug baseline.

Study 4

Sixteen subjects participated in this study. All received 0.15 mg.kg^{-1} morphine i.v. at $t = 0$. Eight subjects received $400 \text{ }\mu\text{g}$ naloxone i.v. at $t = 30 \text{ min}$; eight others received placebo at $t = 30 \text{ min}$. Ventilation was initially measured continuously from $t = 0$ until $t = 90 \text{ min}$. Subsequently measurements were obtained at 30-min intervals until $t = 240 \text{ min}$. The breath-to-breath data were averaged over 1-min periods. Next ensemble averages were obtained and the data was compared to baseline ventilation in a similar fashion as in Study 3.

Study 5

Eight subjects received alfentanil i.v. by Target Controlled Infusion (TCI) using a palm-top computer (Psion 3C, London, UK) programmed with the population pharmacokinetic data set of Maitre *et al.* In this study we used a target plasma alfentanil concentration of 30 ng.ml^{-1} . This concentration was used previously to reduce the hypoxic ventilatory response by 50%. Before the alfentanil infusion and 15 min after a ‘steady-state’ concentration was obtained, we obtained a hypoxic ventilatory response, after which naloxone, $4 \text{ }\mu\text{g.kg}^{-1}$ i.v. ($280 \text{ }\mu\text{g}$ in a 70 kg person), was administered and 15 min later the third and last hypoxic response was obtained. Ten-breath averages were used in the data analysis. The hypoxic sensitivity was calculated by dividing the change in ventilation from normoxia to hypoxia by the change in arterial hemoglobin-oxygen saturation:¹¹

$$\text{Hypoxic sensitivity} = [V_{i, \text{hypoxia}} - V_{i, \text{normoxia}}] / [\text{SpO}_{2, \text{normoxia}} - \text{SpO}_{2, \text{hypoxia}}]$$

(data points derived from the last ten breaths prior to hypoxia and the last ten breaths of hypoxia). Statistical analysis was by one-way analysis of variance with *post-hoc t*-test. *P*-values < 0.05 were considered significant.

Results

All subjects completed the studies without major side effects. The most frequent side effect was nausea and vomiting which occurred in 70% after buprenorphine, 50% after morphine and 0% after alfentanil.

Study 1

The averaged responses of the naloxone ($800 \text{ }\mu\text{g}$) and placebo administration following 0.2 mg buprenorphine are shown in figure 1. At none of the measurement times did these two groups differ in the change in ventilation (or absolute ventilation values, data not shown). In order to detect a small effect of naloxone on ventilation unobserved in the averaged data, we calculated the difference in ventilation from $t = 75$ to $t = 180 \text{ min}$. In the placebo group the change in ventilation was $0.2 \pm 0.5 \text{ l.min}^{-1}$ against $2.2 \pm 0.7 \text{ l.min}^{-1}$ in the naloxone group. This difference did not reach the level of significance ($P = 0.08$, one-tailed *t*-test, assuming a

larger response in the naloxone group). Our data indicate that the buprenorphine effect on ventilation was similar at all times irrespective of 800 μg naloxone infusion at $t = 120$ min.

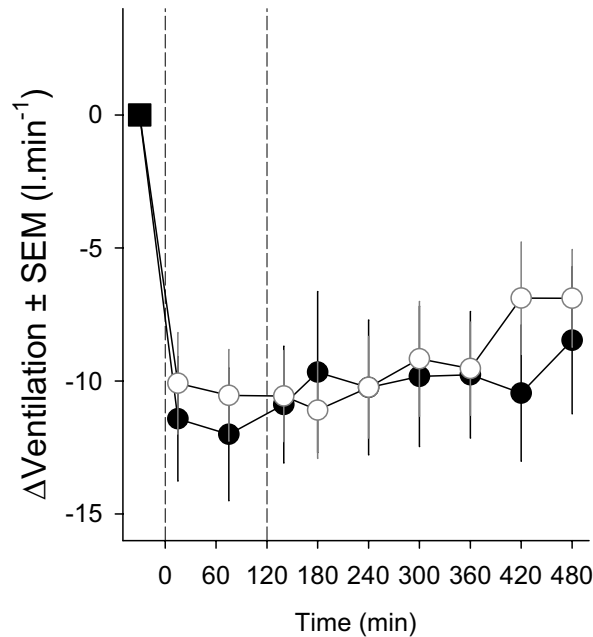


Figure 1. Influence of 800 μg naloxone on 0.2 mg buprenorphine-induced change in ventilation (Δ ventilation). Buprenorphine was given at time $t = 0$ min; naloxone or placebo at time $t = 120$ min. Square is predrug baseline value (0 l.min⁻¹). Closed circles: naloxone ($n = 8$); open circles: placebo ($n = 8$).

Study 2

The mean effect of buprenorphine/placebo on minute ventilation is given in figure 2 (grey area). Baseline ventilation was 24.0 ± 3.3 l.min⁻¹ at a fixed P_{ETCO_2} of 7.0 ± 0.1 kPa. Peak depression of ventilation occurred at $t = 71$ min after the start of the buprenorphine infusion reaching a value of 13.5 ± 1.5 l.min⁻¹. Relative to baseline, peak depression was $62 \pm 11\%$, indicating a reduction of baseline ventilation by 38%. In order to get an impression of the naloxone data, we plotted the data of two subjects given 2 and 6 mg naloxone in figure 2. The subject receiving 2 mg showed full reversal back to baseline (reversal = 1). In contrast, the subject given the higher naloxone dose showed little reversal (reversal = 0.1). In figure 3 we plotted the individual dose–reversal data for the time frame 61–63 min. The data show that full reversal $\pm 20\%$ was obtained at doses between 2 and 4 mg naloxone, but that at higher doses reversal gradually declined. We calculated the naloxone dose causing 50% reversal of 0.95 ± 0.09 mg and the naloxone dose causing the return to 50% depression of 5.2 ± 0.22 mg (data fitted to a sigmoid E_{max} model with inhibitory component, see methods; values are median \pm SE).

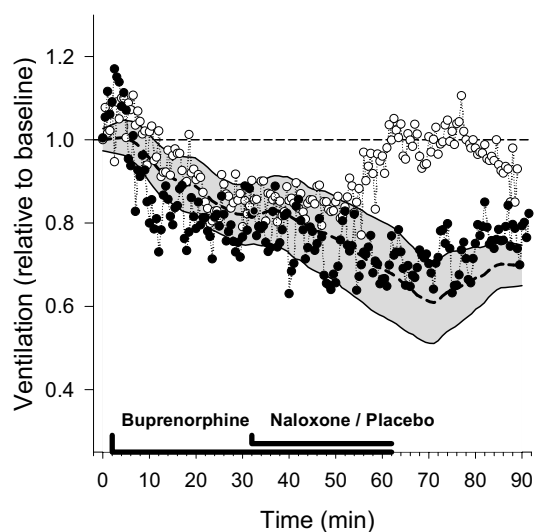


Figure 2. Buprenorphine (0.2 mg given over 60 min) induced respiratory depression. Grey area is the mean \pm SEM of the combination of buprenorphine and placebo ($n = 8$). The individual data (1-min averages) of two subjects receiving the combination of buprenorphine and naloxone are superimposed. Open circles: subject receiving 2 mg naloxone, closed circles: subject receiving 6 mg naloxone. Naloxone or placebo was given over 30 min.

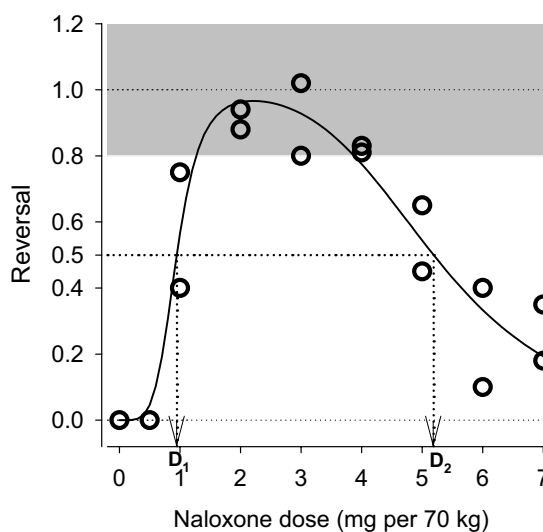


Figure 3. Influence of placebo and 0.5 to 7 mg naloxone reversal on 0.2 mg buprenorphine-induced respiratory depression. Reversal ranges from 0 (no reversal) to 1 (complete reversal). Circles are values of individual subjects (two subjects received 0.5 mg naloxone; 8 subjects placebo). Grey field indicates the area of full reversal \pm 20%. The line through the data is the fit according to the sigmoid E_{\max} function.

Study 3

Baseline ventilation averaged to $21.9 \pm 2.5 \text{ l}\cdot\text{min}^{-1}$ (data from studies 3.1 and 3.2 combined). The effect of both doses of buprenorphine (0.2 and 0.4 mg) were successfully reversed by a continuous infusion of naloxone at the dose chosen by us, which was, at least partly, based on the data from Study 2.

STUDY 3.1. See figure 4. Buprenorphine, 0.2 mg, caused a rapid decrease in ventilation. Prior to naloxone or placebo infusion ($t = 32 \text{ min}$), ventilation was $84 \pm 3\%$ and $79 \pm 5\%$ of baseline, respectively. In the placebo group, ventilation declined further to a nadir of $57 \pm 6\%$ of baseline at $t = 120 \text{ min}$. In the naloxone group, the nadir was $78 \pm 4\%$ of baseline at $t = 48 \text{ min}$ (at the same time ventilation was $61 \pm 5\%$ of baseline in the placebo group). From that point on ventilation increased to reach baseline values (that is baseline ventilation $-1 \times 95\%$ confidence interval) at $t = 70 \text{ min}$. Ventilation remained not different from baseline during the remainder of the naloxone infusion. After termination of the naloxone infusion (at $t = 152 \text{ min}$) ventilation decreased but it never reached the level observed in the placebo group.

STUDY 3.2. See figure 4. A rapid decrease in ventilation occurred after the initiation of the 0.4 mg buprenorphine infusion. Prior to naloxone or placebo infusion ($t = 32 \text{ min}$), ventilation

was $62 \pm 5\%$ and $64 \pm 5\%$ of baseline, respectively. In the placebo group, ventilation declined further to a nadir of $40 \pm 3\%$ of baseline at $t = 150$ min. In the naloxone group, the ventilation nadir was $61 \pm 5\%$ of baseline at $t = 34$ min (ventilation of the placebo group was $66 \pm 7\%$ at $t = 34$ min). From that point on ventilation increased to reach baseline values at $t = 93$ min. Ventilation remained not different from baseline during the remainder of the naloxone infusion. After termination of the naloxone or placebo infusion (at $t = 152$ min) the changes in ventilation were similar to those observed in Study 3.1.

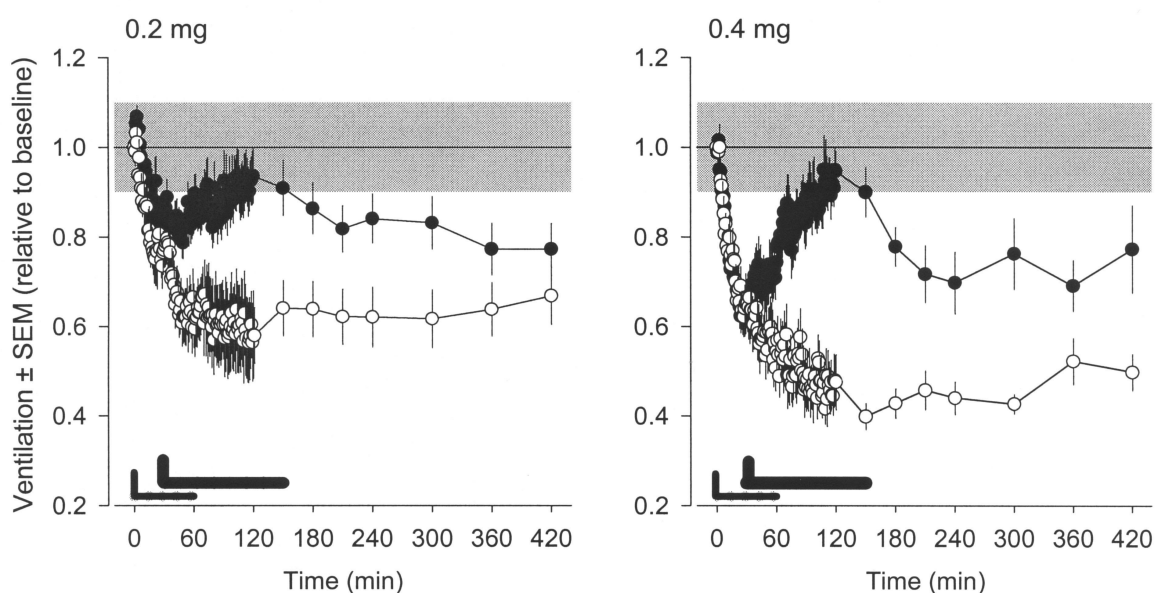


Figure 4. Influence of a continuous infusion of naloxone and placebo on 0.2 mg buprenorphine- (left) and 0.4 mg buprenorphine-induced respiratory depression (right). The buprenorphine dose was given over 60 min from $t = 2$ to $t = 62$ min. Naloxone or placebo was given for 2 h, from $t = 32$ to $t = 152$ min. Closed circles: naloxone ($n = 8$); open circles: placebo ($n = 8$). The grey area represents the 95% confidence interval of predrug baseline ventilation.

Study 4

See figure 5. Morphine, $0.15 \text{ mg}\cdot\text{kg}^{-1}$, caused a rapid decrease in ventilation (baseline = $20.4 \pm 1.0 \text{ l}\cdot\text{min}^{-1}$). Prior to infusion of naloxone and placebo, ventilation was reduced to 14.1 ± 0.6 and $12.4 \pm 1.5 \text{ l}\cdot\text{min}^{-1}$ in the naloxone and placebo groups, respectively. While placebo had little effect on ventilation, $400 \mu\text{g}$ naloxone caused a rapid return of ventilation to baseline. Ventilation was not different from baseline from $t = 37$ to $t = 66$ min, after which it gradually returned towards placebo-levels.

Study 5

The predrug hypoxic sensitivity was $1.22 \pm 0.21 \text{ l}\cdot\text{min}^{-1}\cdot\%^{-1}$. Alfentanil caused the severe impairment of the hypoxic sensitivity (reduction $> 50\%$ to $0.48 \pm 0.35 \text{ l}\cdot\text{min}^{-1}\cdot\%^{-1}$; $P < 0.05$

versus predrug control and naloxone) which was fully restored by $4 \mu\text{g.kg}^{-1}$ naloxone ($1.15 \pm 0.29 \text{ l.min}^{-1}.\%^{-1}$; n.s. versus control).

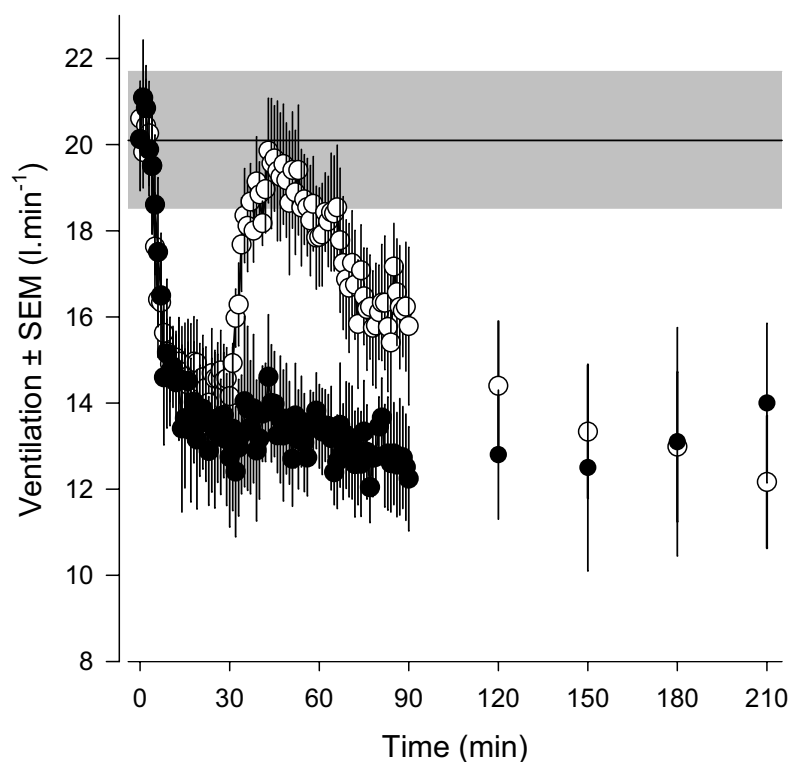


Figure 5. Influence of $400 \mu\text{g}$ naloxone or placebo (given at $t = 30 \text{ min}$) on 0.15 mg.kg^{-1} morphine-induced respiratory depression. Open circles are naloxone data ($n = 8$); closed circles placebo ($n = 8$). Grey area is the mean predrug ventilation $\pm 95\%$ confidence interval.

Discussion

In our studies, we observed that, while 0.4 mg i.v. naloxone (given in 90 s) caused full reversal of morphine- and alfentanil-induced respiratory depression (both are full μ -opioid receptor agonists), a double dose of naloxone (0.8 mg) had no effect on respiratory depression induced by the opioid analgesic buprenorphine. We next explored the naloxone dose–response relationship and observed that increasing doses of naloxone caused full reversal of 0.2 mg buprenorphine-induced respiratory depression ($2\text{--}4 \text{ mg}$ naloxone given in 30 min). Further increasing the naloxone dose ($5\text{--}7 \text{ mg}$), however, caused a decline in reversal activity. The form of the dose–response relationship is best described by a bell-shape or inverse U. Taken into account these data, we designed a naloxone infusion scheme intended to cause full reversal of the respiratory depression from 0.2 and 0.4 mg buprenorphine. A naloxone bolus dose of 2 to 3 mg , followed by a continuous infusion of 4 mg.h^{-1} , caused full reversal within

40 to 60 min. Renarcotization did occur upon the termination of the naloxone infusion. These data indicate that reversal of buprenorphine-induced respiratory depression is only possible (i) with a continuous infusion of naloxone and (ii) with a specific naloxone dose chosen based on the buprenorphine dose and the form of the naloxone dose–response curve.

All opioids that interact with the μ -opioid receptor system depress respiration.¹² Buprenorphine is no exception to that rule. The extent of respiratory effect is highly variable and is related to the specific opioid, the opioid dose, the administration mode, concurrent medication, underlying disease, pain and the state of arousal (these two factors vary over time), genetics and exogenous stimulatory factors. Since the occurrence of overt and sometimes life-threatening respiratory depression is often unpredictable, the ability to induce rapid opioid reversal is of evident importance. In contemporary medicine, naloxone has become the drug of choice for treatment of opioid-induced respiratory depression. Naloxone is a non-specific opioid receptor antagonist (*i.e.*, it antagonizes the μ -, κ - and δ -opioid receptor) with a relatively short duration of action resulting from rapid elimination; its half-life in plasma is about 30–45 min.¹³

Although there is ample evidence that buprenorphine, just like other μ -opioid receptor agonists, produces significant respiratory depression at clinical doses (see figures 1, 2 and 4), sparse data from the literature addressed the issue of reversal of buprenorphine-induced respiratory depression.^{5–7} The picture that emerges from these few studies is that at relatively large bolus naloxone doses little (that is, just partial) reversal of buprenorphine's respiratory effects is observed. For example a recent short report indicated that an incremental naloxone dose of 2.4 mg has an effect on 0.4 mg buprenorphine-induced respiratory depression no greater than placebo in patients during sevoflurane/nitrous oxide anesthesia.⁷ An older study by Gal showed only partial reversal of 0.3 mg buprenorphine-induced respiratory depression with 5 and 10 mg *i.v.* naloxone (given as single bolus).⁵ The inability to obtain full reversal in these two studies may be related to various factors, such as: anesthesia (anesthesia must be considered a serious complication when studying opioid-induced respiratory depression due to the complex opioid–anesthetic interaction on breathing),^{14,15} the lack of sensitivity of the respiratory model applied to assess naloxone–buprenorphine interaction, the use of single naloxone doses and finally the use of a too high dose of naloxone (see figure 3).

The resistance to naloxone reversal is related to the very high affinity of buprenorphine for the μ -opioid receptor.¹³ This very high affinity explains why relatively high doses of naloxone (2–4 mg) are needed before complete reversal is observed. The need for a continuous infusion in this process (upon termination of the naloxone infusion there was a rapid return of respiratory depression, see figure 4) implies the need for continuous supply of naloxone to the opioid receptor sites in the brain involved in respiratory depression. Otherwise the naloxone bolus is rapidly washed out from the brain compartment and eliminated from the body. We believe that the use of a single dose naloxone infusion to reverse opioid-related overdose has several disadvantages which are unrelated to the opioid involved: renarcotization due to

naloxone's short duration of action (in case of morphine see figure 5), the inability to titrate to effect causing the return of pain and sympathico-excitation. An infusion regimen aimed at a prolonged and steady-state naloxone plasma concentration may overcome these shortcomings. For example, continuous (11 h) naloxone infusion after high-dose fentanyl anesthesia caused reversal of respiratory depression without causing reanarcotization, pain, or sympathico-excitation.¹⁶

An interesting observation in Studies 3.1 and 3.2 is the higher ventilation levels after naloxone treatment than after placebo treatment at times when naloxone is washed out from the brain and possibly also from the body (see figure 4 at $t > 240$ min). This is probably due to washout from the brain compartment of buprenorphine that was replaced by naloxone at the μ -opioid receptor or at non-specific binding sites (*i.e.*, some buprenorphine was lost without replacement). A similar observation was not made for morphine (figure 5). This may suggest that the morphine, which accumulates at intracellular sites in the brain,¹⁷ fully replaces the morphine which was washed-out after naloxone-replacement at the receptor.

Naloxone doses exceeding the maximal effective dose (> 4 mg) lead to a decrease in (0.2 mg) buprenorphine reversal efficacy (figure 3). Since the number of subjects was limited (just 2 subjects per naloxone dose over the dose range from 0.5–7 mg) we consider this observation preliminary. Evidently, further studies are needed. In a first attempt, we performed a set of experiments after 0.4 mg buprenorphine and applied various naloxone doses (1 dose per subject; duration of naloxone infusion 30 min) and observed a similar bell-shaped dose–response relationship albeit full reversal was not reached (Dahan, unpublished observation). Our unexpected observation may be specific to the naloxone molecule or to buprenorphine and its interaction with naloxone. If it is just a naloxone effect, our data suggest that naloxone turns from a full antagonist to an agonist at high dose. We are unaware of any studies on increasing doses of naloxone on opioid-analgesia or opioid-side effects. Buprenorphine *per se* has a long history of showing bell-shaped dose–response curves with respect to its analgesic and side effect profile.^{1,18} Most of these observations were made in animals. For example, rodents display a bell-shape buprenorphine dose–response relationship in various antinociceptive assays (electrical pain, heat pain, visceral pain and spinal nerve ligation) and on respiratory depression (using arterial PCO_2 as end point).¹⁹⁻²¹ Also in humans there are indications of the existence of a bell-shaped dose–response curve with respect to analgesia. For example, two patients treated with buprenorphine ($30\text{--}40 \mu\text{g}\cdot\text{kg}^{-1}$) for postoperative pain showed improved pain relief after 0.4 mg naloxone infusion, probably due to shifting of the bell-shaped dose–analgesia curve to the right.²² A rightward-shift of the bell-shaped buprenorphine dose–response curve after the infusion of an opioid-antagonist (naltrexone) has been observed in rats using an electrical pain test.¹⁹ Note that a bell-shaped curve was actually never observed in experimental human studies and clinically complete analgesia is reached with buprenorphine. The mechanism of the bell-shape curve remains unknown. Some argued that the form of the curve is related to the type and intensity of (experimental) pain administered.²¹ Others suggested non-competitive autoinhibition, in which there are two

receptor subpopulations, one mediating the agonistic properties at low dose, the other mediating the antagonistic properties at high dose.^{3,19,21,23} Finally, Lutfy *et al.*²⁴ suggest the contribution of the ORL₁ receptor. They showed that buprenorphine, but not morphine, given to mice activates ORL₁ receptors, compromising (antagonizing) analgesia from μ -opioid receptors. The latter theory seems not plausible taken into account that the scanty literature which exists on the respiratory effects of stimulation of ORL₁ receptors shows respiratory depression rather than stimulation.²⁵ The existence of two μ -opioid receptor subpopulations as described above could also theoretically explain our findings with high-dose naloxone causing the antagonism of the receptors mediating the antagonistic effects of buprenorphine. We are not aware, however, of any observation of these two receptor subpopulations in *in vitro* or *in vivo* animal studies.

We studied respiration in a group of healthy young volunteers and not in patients of various ages with pain. Hence, we remain uninformed what the effect of the naloxone–buprenorphine interaction is on pain and respiration in acute and chronic pain patients. Clinical studies in patients on buprenorphine treatment will be necessary to elucidate these important matters.

Finally, studying the ability to reverse opioid-induced side effects is not only relevant to compounds with high affinity for the μ -opioid receptor, such as buprenorphine. Since only few studies addressed the issue of long-term opioid reversal, we believe that more studies are required to assess –in case of respiratory depression– the specific dose and administration mode of naloxone needed to restore breathing and maintain it at an adequate level. This is relevant to opioids given at high dose, long acting opioids and opioids given as a continuous infusion (*e.g.*, using the transdermal patch formulation).

References

1. Cowan A, Friderichs E, Straßburger W, Raffa RB. Basic pharmacology of buprenorphine. In: Budd K, Raffa RB, eds. Buprenorphine – The unique opioid analgesic. Stuttgart, Georg Thieme Verlag KG, 2005; 3-21
2. Weinhold LL, Preston KL, Farre M, Lienson IA, Bigelow GE. Buprenorphine alone and in combination with naloxone in non-dependent humans. *Drug and Alcohol Dependence* 1992; 30: 263-74
3. Boas RA, Villiger JW. Clinical actions of fentanyl and buprenorphine: the significance of receptor binding. *Br J Anaesth* 1985; 57: 192-6
4. Dahan A, Yassen A, Bijl H, Romberg R, Sarton E, Teppema L, Olofsen E, Danhof M. A comparison of the respiratory effects of intravenous buprenorphine and fentanyl in humans. *Br J Anaesth* 2005; 96: 825-34
5. Gal TJ. Naloxone reversal of buprenorphine-induced respiratory depression. *Clin Pharmacol Ther* 1989; 45: 66-71
6. Bowdle TA. Pharmacology of analgesia. In: Healy TEJ, Knight PR, eds. Wylie and Churchill-Davidson's A practice of anesthesia, 7th ed. London, Arnold, 2003; 543-63
7. Mehta V, Phillips JP, Wantman AC, Ratcliffe SH, van Raders PA, Langford RM. Investigation of buprenorphine-induced respiratory depression in anaesthetized patients and its reversibility (abstract). *Br J Anaesth* 2005; 94: 399-400P
8. Drummond GB, Davie IT, Scott DB. Naloxone: dose-dependent antagonism of respiratory depression by fentanyl in anaesthetized patients. *Br J Anaesth* 1977; 49: 151-4

9. Dahan A, DeGoede J, Berkenbosch A, Olivevier ICW. The influence of oxygen on the ventilatory response to carbon dioxide in man. *J Physiol (Lond)* 1990; 428: 485-99
10. Dahan A, Berkenbosch A, DeGoede J, van den Elsen M, van Kleef JW. Influence of hypoxic duration and post-hypoxic inspired O₂ concentration on short term potentiation of breathing in man. *J Physiol (Lond)* 1995; 488: 803-13
11. Dahan A, Sarton E, van den Elsen M, Teppema L, Berkenbosch A, van Kleef J. The ventilatory response to hypoxia in humans: influences of subanesthetic desflurane. *Anesthesiology* 1996; 85: 60-8
12. Dahan A, Sarton E, Teppema L, Olivevier C, Nieuwenhuijs D, Matthes HWD, Kieffer BL. Anesthetic potency and influence of morphine and sevoflurane on on respiration in μ -opioid receptor knockout mice. *Anesthesiology* 2001, 94: 824-32
13. Berkowitz BA, Ngai SH, Hempstead J, Spector S. Disposition of naloxone: use of a new radioimmunoassay. *J Pharmacol Exp Ther* 1975; 195: 499-504
14. Dahan A, Nieuwenhuijs D, Olofsen D, Sarton E, Romberg R, Teppema L. Response surface modeling of alfentanil-sevoflurane interaction on cardiorespiratory control and bispectral index. *Anesthesiology* 2000; 94: 982-91
15. Nieuwenhuijs D, Olofsen E, Romberg R, Sarton E, Ward DS, Engbers F, Vuyk J Teppema L, Dahan A. Response surface modeling of remifentanil-propofol interaction on cardiorespiratory control and bispectral index. *Anesthesiology* 2003; 98: 313-22
16. Takahashi M, Sugiyama K, Hori M, Chiba S, Kusaka K. Naloxone reversal of opioid anesthesia: clinical evaluation and plasma concentrations of continuous naloxone infusion after anesthesia with high-dose fentanyl. *J Anesth* 2004; 18: 1-8
17. Bouw MR, Gårdmark M, Hammerlund-Udenaes M. Pharmacokinetic-pharmacodynamic modeling of morphine-transport across the blood-brain barrier as a cause of the antinociceptive effect delay in rats: a microdialysis study. *Pharm Res* 2000; 17: 1220-7
18. Evans HC, Easthope SE. Transdermal buprenorphine. *Drugs* 2003; 63: 1999-2010
19. Dum JE, Herz A. In vivo receptor binding of the opiate partial agonist, buprenorphine, correlated with its agonistic and antagonistic actions. *Br J Pharmacol* 1981; 74: 627-33
20. Doxey JC, Everitt JE, Frank LW, MacKenzie JE. A comparison of the effects of buprenorphine and morphine on the blood gases of conscious rats. *Br J Pharmacol* 1982; 75: 118
21. Christoph T, Kögel B, Schiene K, Méen M, De Vry J, Friderichs E. Broad analgesic profile of buprenorphine in rodent models of acute and chronic pain. *Eur J Pharmacol* 2005; 507: 87-98
22. Pedersen JE, Chraemmer-Jørgensen, Schmidt JF, Risbo A. Naloxone – a strong analgesic in combination with high-dose buprenorphine? *Br J Anaesth* 1985; 57: 1045-6
23. Villiger JW, Taylor KM. Buprenorphine characteristics of binding sites in the rat central nervous system. *Life Sci* 1981; 29: 2699-708
24. Lutfy K, Eitan S, Bryant CD, Yang YC, Saliminejad N, Walwyn W, Kieffer BL, Takeshima H, Carroll FI, Maidment NT, Evans CJ. Buprenorphine-induced antinociception is mediated by μ -opioid receptors and compromised by concomitant activation of opioid-receptor-like receptors. *J Neurosci* 2003; 23: 10331-7
25. Takita K, Morimoto Y, Kemmotsu O. Roles of nociceptin/orphanin FQ and nociceptin/orphanin FQ peptide receptor in respiratory rhythm generation in the medulla oblongata: an in vivo study. *Br J Anaesth* 2003; 91: 385-9

