

Naloxone Reversal of Buprenorphine-induced Respiratory Depression

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Background: The objective of this investigation was to examine the ability of the opioid antagonist naloxone to reverse respiratory depression produced by the μ -opioid analgesic, buprenorphine, in healthy volunteers. The studies were designed in light of the claims that buprenorphine is relatively resistant to the effects of naloxone.

Methods: In a first attempt, the effect of an intravenous bolus dose of 0.8 mg naloxone was assessed on 0.2 mg buprenorphine-induced respiratory depression. Next, the effect of increasing naloxone doses (0.5–7 mg, given over 30 min) on 0.2 mg buprenorphine-induced respiratory depression was tested. Subsequently, continuous naloxone infusions were applied to reverse respiratory depression from 0.2 and 0.4 mg buprenorphine. All doses are per 70 kg. Respiration was measured against a background of constant increased end-tidal carbon dioxide concentration.

Results: An intravenous naloxone dose of 0.8 mg had no effect on respiratory depression from buprenorphine. Increasing doses of naloxone given over 30 min produced full reversal of buprenorphine effect in the dose range of 2–4 mg naloxone. Further increasing the naloxone dose (doses of 5 mg or greater) caused a decline in reversal activity. Naloxone bolus doses of 2–3 mg, followed by a continuous infusion of 4 mg/h, caused full reversal within 40–60 min of both 0.2 and 0.4 mg buprenorphine-induced respiratory depression.

Conclusions: Reversal of buprenorphine effect is possible but depends on the buprenorphine dose and the correct naloxone dose window. Because respiratory depression from buprenorphine may outlast the effects of naloxone boluses or short infusions, a continuous infusion of naloxone may be required to maintain reversal of respiratory depression.

LONG-ACTING opioids are important tools in the treatment of postoperative acute pain and chronic cancer and noncancer pain. When selecting one of the available compounds, not only the analgesic properties but also the safety profile of the drug must 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, opioid receptor-like 1 receptor-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, 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 as compared with other opioids.³ After an intravenous infusion of 0.2–0.4 mg/70 kg, the duration of action of buprenorphine is approximately 6–8 h. Data obtained in opioid-naïve volunteers indicate that buprenorphine causes dose-dependent respiratory depression that levels off at greater buprenorphine doses (*i.e.*, plateau or ceiling of 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 1980s as well as some anecdotal data suggest that the respiratory depression from buprenorphine is resistant to antagonism by naloxone.^{5–7} Relatively low bolus doses of intravenous naloxone had no effect, whereas high doses (2.5–10 mg) caused only partial reversal of the respiratory effects of buprenorphine. 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 intravenous 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 intravenous buprenorphine-induced respiratory depression. 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

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assessed the effect of a continuous naloxone (or placebo) infusion on 0.2 and 0.4 mg intravenous buprenorphine-induced respiratory depression.

Materials and Methods

Subjects

A total of 67 male and female subjects (age range, 20–30 yr; weight, 54–93 kg) participated in and completed the studies after approval of the protocols was obtained from the Human Medical Ethics Committee (Commissie Medische Ethiek, Leiden University Medical Center, Leiden, The Netherlands). 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 before the study. They were comfortably seated in a hospital bed for the duration of the study. They were naive with respect to the nature of the studies but were informed regarding the risk of participating. All subjects were students at Leiden University and received a financial reimbursement for their participation (€75–100 depending on the study).

Apparatus

Inspired and expired gas flows were measured with a pneumotachograph (Hans Rudolph, Myandotta, MI) 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 1,000 ml, at a frequency of 20/min). The pneumotachograph was connected to a T-piece. One arm of the T-piece received a gas mixture with a flow of 45 l/min from a gas mixing system, consisting of three mass flow controllers (Bronkhorst High Tech BV, Veenendaal, The Netherlands) with which the flow of oxygen, carbon dioxide, and nitrogen 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 ($P_{ET}O_2$ and $P_{ET}CO_2$, respectively) to follow a specified pattern in time, independent of the ventilatory response (*i.e.*, dynamic end-tidal forcing).⁹ In studies 1–3, end-tidal partial pressure of carbon dioxide (P_{CO_2}) was clamped at 53 mmHg throughout the measurements (approximately 8 kPa above resting values), while end-tidal partial pressure of oxygen (P_{O_2}) was maintained at a normoxic value of 110 mmHg. The oxygen and carbon dioxide concentrations and the arterial hemoglobin-oxygen saturation were measured with a Datex Multicap

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

Study Design and Data Analysis

The studies were placebo-controlled and had a double blind design. The local pharmacy delivered the buprenorphine hydrochloride (Reckitt Benckiser Healthcare Ltd., Hull, United Kingdom), naloxone hydrochloride (manufactured by the pharmacy), and placebo (0.9% NaCl). Randomization and preparation of the syringes was performed by a physician not involved in the study.##

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 reported are mean \pm SEM, unless otherwise stated.

Study 1. Sixteen subjects participated in this study. All received 0.2 mg intravenous buprenorphine (at $t = 0$) followed by 800 μ g naloxone (in eight subjects) or placebo (in eight subjects) at $t = 120$ min. At the following time periods, steady state ventilation (V_i) was measured (measurement period 7 min): –10 min (10 min before drug infusion), 15, 75, 140, 180, 240, 300, 360, 420, and 480 min. Analysis of variance and *post hoc 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 at $t = 2$ min, followed by a continuous infusion for 1 h of 0.1 mg/h (total dose = 0.2 mg in 60 min). At $t = 32$, x mg naloxone was given, one half as bolus and one half infused over 30 min. The following total naloxone doses (x) were tested: 0, 0.5, 1, 2, 3, 4, 5, 6, and 7 mg. Each dose was tested in two subjects, except for placebo, which was tested in eight subjects. Breathing was measured continuously from 2 min before buprenorphine infusion until 90 min after the start of infusion.

The breath-to-breath data were averaged over 1-min periods. An ensemble average (mean of the 1-min subject means) 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 time points. To quantify the respiratory effect of naloxone relative to placebo, we used the following formula on the data of each subject who had received the buprenorphine–naloxone combination:

Randomization lists obtained from www.randomization.com were used in our studies. Accessed March 17, 2006.

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

where time 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); $V_{\text{placebo}}(z)$ is mean minute ventilation in the placebo group during period z , $V_{\text{naloxone}}(z)$ is mean ventilation of the equivalent time period after naloxone, and V_{baseline} is mean ventilation of the 2 min before the buprenorphine infusion. This analysis will yield a quantitative measure of reversal, with 0 indicating no reversal (naloxone no better than placebo) and 1 indicating full reversal (response returned to pre-buprenorphine level).

Study 3. Thirty-two subjects participated in this study.

Study 3.1. Sixteen received 0.1 mg intravenous buprenorphine at time $t = 2$ min, followed by a continuous infusion for 1 h of 0.1 mg/h (total dose = 0.2 mg in 60 min). At time $t = 32$ min, 2 mg naloxone ($n = 8$) or placebo ($n = 8$) was infused, followed by a continuous infusion of 4 mg/h for 2 h.

Study 3.2. Sixteen other subjects received 0.2 mg intravenous buprenorphine at time $t = 2$ min, followed by a continuous infusion for 1 h of 0.2 mg/h (total dose = 0.4 mg in 60 min). At time $t = 32$ min, 3 mg naloxone ($n = 8$) or placebo ($n = 8$) was infused, followed by a continuous infusion of 4 mg/h for 2 h. The bolus naloxone dose was 50% greater than that of study 3.1. This was based on a pilot study in three subjects that showed the need for a greater initial dose of naloxone after 0.4 mg but not after 0.2 mg buprenorphine.

Ventilation was initially measured continuously from 2 min before 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 in the naloxone and placebo data groups. The values were compared with 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 predrug baseline.

Results

All subjects completed the studies without major side effects. The most frequent side effects were sedation (which occurred in all subjects) and nausea (which occurred in 46 of the 67 subjects).

Study 1

In the placebo group, buprenorphine decreased ventilation from 24.2 ± 1.7 l/min to 13.6 ± 3.4 l/min at $t = 75$ min; in the naloxone group, ventilation decreased

from 26.5 ± 2.1 l/min to 14.4 ± 1.7 l/min at $t = 75$ (not significant, analysis of variance). After infusion of 800 μg naloxone, ventilation at none of the measurement times differed between placebo and naloxone groups (analysis of variance). To detect a small effect of naloxone on ventilation unobserved in the pooled data analysis, we calculated the difference in ventilation from $t = 75$ to $t = 180$ min. In the placebo group, the change in ventilation was 0.2 ± 0.5 l/min, *versus* 2.2 ± 0.7 l/min 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).

Study 2

The mean effect of buprenorphine-placebo on minute ventilation is given in figure 1 (gray area). Baseline ventilation was 24.0 ± 3.3 l/min at a fixed end-tidal PCO_2 of 52.9 ± 0.9 mmHg. 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. Relative to baseline, peak depression was $62 \pm 11\%$ of baseline, indicating a reduction of baseline ventilation by 38%. To get an impression of the naloxone data, we plotted representative data of two subjects given 2 and 6 mg naloxone in figure 1. 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 2, we plotted the individual dose-reversal data for 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 (data fitted to a sigmoid Emax model with inhibitory component—see legend of fig. 2—values are median \pm SE) and the dose causing the return to 50% depression of 5.20 ± 0.94 mg naloxone.

Study 3

Baseline ventilation averaged to 21.9 ± 2.5 l/min (data from studies 3.1 and 3.2 combined). The effects 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 3A. Buprenorphine, 0.2 mg, caused a rapid decrease in ventilation. Before naloxone or placebo infusion ($t = 32$ min), ventilation was 84 ± 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 $t = 120$ min. In the naloxone group, the nadir was $78 \pm 4\%$ of baseline at $t = 48$ min (at the same time period, ventilation was $61 \pm 5\%$ of baseline in the placebo group). From that point on, ventilation increased to reach baseline values (*i.e.*, baseline ventilation $- 1 \times 95\%$ confidence interval) at $t = 70$ min. Ventila-

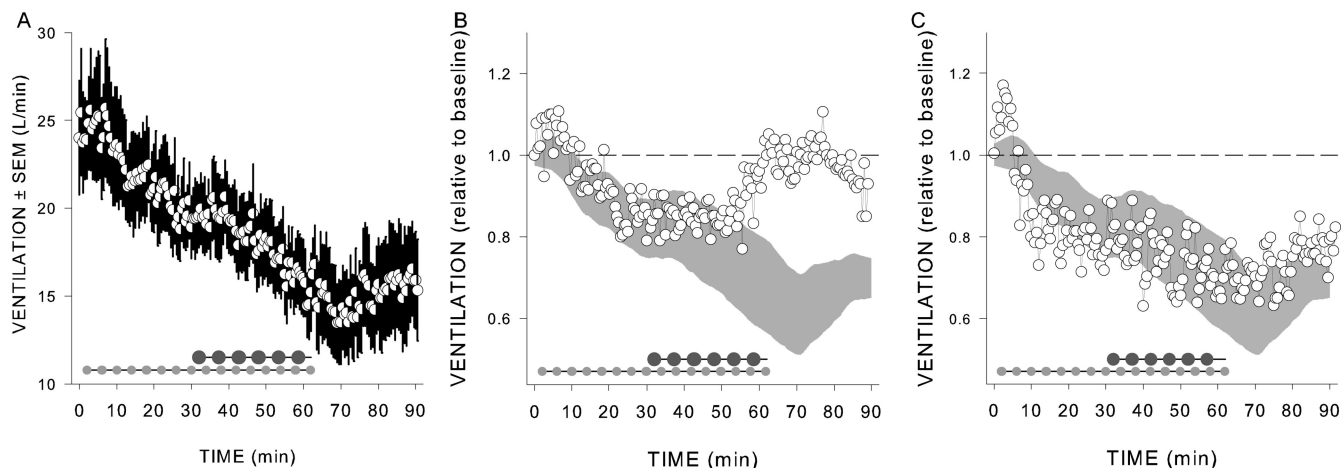


Fig. 1. (A) Effect of placebo on 0.2 mg buprenorphine-induced respiratory depression. Values are the mean values \pm SEM ($n = 8$) of the 1-min averages of individual subjects. (B) Influence of 2 mg naloxone given over 30 min on 0.2 mg buprenorphine-induced respiratory depression (open circles) in one subject. Gray field in the background is the result of the placebo group. (C) Influence of 6 mg naloxone given over 30 min on 0.2 mg buprenorphine-induced respiratory depression (open circles) in one subject. Gray field in the background is the result of the placebo group. Light gray dots = buprenorphine infusion; dark gray dots = naloxone infusion.

tion remained not different from baseline during the remainder of the naloxone infusion. After termination of the naloxone infusion (at $t = 152$ min), ventilation decreased, but it never reached the level observed in the placebo group.

Study 3.2. See figure 3B. A rapid decrease in ventilation occurred after the initiation of the 0.4 mg buprenorphine infusion. Before naloxone or placebo infusion ($t = 32$ min), ventilation was 62 ± 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.

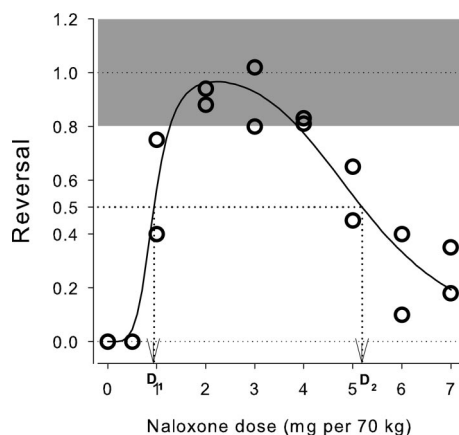


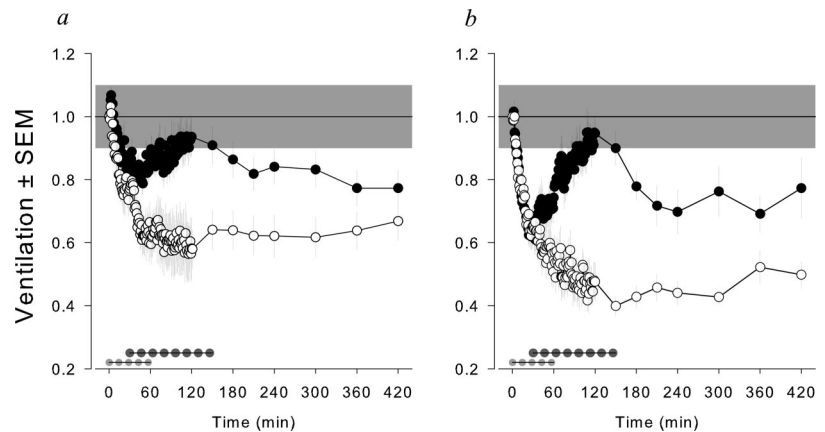
Fig. 2. Influence of 0 (placebo) and 0.5–7 mg naloxone on 0.2 mg intravenous buprenorphine-induced respiratory depression. Reversal (see equation 1) ranges from 0 (effect not different from placebo) to 1 (reversal to predrug baseline level). Circles are values of individual subjects (2 subjects received 0.5 mg naloxone, 8 subjects received placebo). Gray field indicates the area of full reversal $\pm 20\%$. Note the biphasic nature of the naloxone response. To guide the eye, a sigmoid Emax function incorporating an inhibitory component was fitted through the data (using NONMEM) of the form $Y = X_1^\gamma / (1 + X_1^\gamma) \cdot [1 / (1 + X_2^\gamma)]$, where $Y =$ reversal, $X_1 =$ dose / D_1 , $X_2 =$ dose / D_2 , D_1 is the naloxone dose causing 50% reversal, and D_2 is the naloxone dose causing the return to 50% depression. Values obtained are $D_1 = 0.95 \pm 0.09$ mg, $D_2 = 5.20 \pm 0.94$ mg, and $\gamma = 4.77 \pm 0.22$.

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

Discussion

In our studies, we observed that an intravenous dose of naloxone of 0.8 mg had no effect on respiratory depression induced by the opioid analgesic buprenorphine. We next explored the naloxone dose–response relation and observed that increasing doses of naloxone caused full reversal of buprenorphine respiratory depression (2–4 mg naloxone given in 30 min). Further increasing the naloxone dose (5–7 mg), however, caused a decline in reversal activity. The form of the dose–response relation is best described by a bell shape or inverse U. Taking 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 2–3 mg, followed by a continuous infusion of 4 mg/h, caused full reversal within 40–60 min. Renarcotization did occur upon the termination of the naloxone infusion. These data indicate that reversal of buprenorphine-induced respiratory depression is possible but depends on the naloxone dose and its inverse U-shaped dose–response relation. That is, reversal is possible within a specific naloxone dose window. Furthermore, because respiratory depression from buprenorphine may outlast the effects of naloxone boluses

Fig. 3. Influence of a continuous infusion of naloxone and placebo on 0.2 mg intravenous buprenorphine (A) and 0.4 mg intravenous buprenorphine (B). The buprenorphine dose was given over 60 min from $t = 2$ to $t = 62$ min (light gray dots). Naloxone or placebo was given for 2 h, from $t = 32$ to $t = 152$ min (dark gray dots). Black circles = naloxone ($n = 8$ per treatment); open circles = placebo ($n = 8$ per treatment). The gray area represents the 95% confidence interval of predrug baseline ventilation. Mean ventilation data are relative to baseline.



or short infusions, a continuous infusion of naloxone may be required to maintain reversal of respiratory depression. Note that the design of studies 2 and 3 was such that it mimics the clinical situation in which a possible respiratory effect from a buprenorphine transdermal patch must be reversed by naloxone. A subcutaneous depot of buprenorphine will persist upon the removal of the patch. During the existence of this depot and the need for reversal, naloxone and buprenorphine will then be released or administered simultaneously to the blood (as they are in studies 2 and 3).

All opioids that interact with the μ -opioid receptor system depress respiration.¹¹ 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. Because 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 nonspecific opioid receptor antagonist (*i.e.*, it antagonizes the μ -, κ -, and δ -opioid receptors) with a relatively short duration of action resulting from rapid elimination; its half-life in plasma is approximately 30–45 min.¹²

There is ample evidence that buprenorphine, like other μ -opioid receptor agonists, produces significant respiratory depression at clinical doses (figs. 1 and 3), although we recently showed that buprenorphine-induced respiratory depression, unlike other μ -opioids, shows an apparent maximum in effect (ceiling).^{4,13} Interestingly, only 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 (*i.e.*, only partial) reversal of the respiratory effects of buprenorphine is observed. For example, a recent short report indicates 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 Gal⁵ showed only partial reversal of 0.3 mg buprenorphine with 5 and 10 mg intravenous naloxone (given as single bolus). 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 (fig. 2).

The resistance to naloxone reversal is related to the high affinity of buprenorphine for the μ -opioid receptor.^{1,3} This high affinity explains why relatively high doses of naloxone (2–4 mg) are needed before 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; fig. 3) 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 of naloxone infusion to reverse opioid-related overdose has several disadvantages that are unrelated to the opioid involved: re-narcotization due to the short duration of action of naloxone, the inability to titrate to effect causing the return of pain, and sympathicoexcitation. 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 re-narcotization, pain, or sympathicoexcitation.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 (fig. 3 at $t > 240$ min). This is probably due to washout from the brain compartment of buprenorphine which was replaced by naloxone at the μ -receptor or at nonspecific binding sites (*i.e.*, some buprenorphine was lost without replacement).

Naloxone doses exceeding the maximal effective dose (> 4 mg) lead to a decrease in (0.2 mg) buprenorphine reversal efficacy (fig. 2). Because the number of subjects was limited (just two subjects per naloxone dose over the dose range from 0.5 to 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 (one dose per subject; duration of naloxone infusion 30 min) and observed a similar bell-shaped dose-response relation, albeit full reversal was not reached (A. Dahan, unpublished observation, September 2004–January 2005). Our unexpected observation is most probably specific to buprenorphine and its interaction with naloxone. Buprenorphine has a long history of showing bell-shaped dose-response curves with respect to its analgesia and side effect profile.¹ Most of these observations were made in animals. For example, rodents display a bell-shaped buprenorphine dose-response relation in various antinociceptive assays (electrical pain, heat pain, visceral pain, and spinal nerve ligation).^{17,18} 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 (30–40 $\mu\text{g}/\text{kg}$) 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.¹⁹ 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.²⁰ Note that a bell-shaped curve was never observed in experimental human studies, and clinically complete analgesia is reached with buprenorphine. The mechanism of the bell-shaped curve remains unknown. Some argued that the form of the curve is related to the type and intensity of (experimental) pain administered.²⁰ Others suggested noncompetitive 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.^{3,17,18,20} Finally, Lutfy *et al.*²¹ suggest the contribution of the opioid receptor-like 1 receptor. They showed that buprenorphine, but not morphine, given to mice activates opioid receptor-like 1 receptors, compromising (antagonizing) analgesia from μ -opioid receptors. The latter theory seems not plausible when one takes into account that the scanty literature that exists on the respiratory effects of stimulation of opioid receptor-like 1 receptors shows respiratory depression rather than stimulation.²² The existence of two

μ -opioid receptor subpopulations as described above could 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.

The results of our studies demonstrate that the specific dose and mode of administration of naloxone to restore breathing and maintain it at an adequate level are complex matters that require further study. Our data show that even after administration of large boluses of naloxone or boluses plus brief infusions, respiratory depression induced by buprenorphine recurred and persisted for the duration of the study (7 h in study 3). Additional studies are required to define the dose and the mode of administration of naloxone to restore breathing and maintain it at an adequate level in the clinical setting, which is complicated by acute and chronic pain, gender effects,²³ high doses of opioids, long-acting opioids, and various sustained-release preparations of opioids.

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