Lack of Effect of Single High Doses of Buprenorphine on Arterial Blood Gases in the Rat

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High dose buprenorphine, a potent semisynthetic agonist-antagonist for opiate receptors, is now used in substitution treatment of human heroin addiction. Deaths have been reported in addicts misusing buprenorphine. We determined the median lethal dose (LD₅₀) and studied the effects of high doses of intravenous buprenorphine on arterial blood gases in rats. Male Sprague-Dawley rats were administered buprenorphine intravenously to determine the LD₅₀ using the up-and-down method. Subsequently, catheterized groups of 10 restrained rats received no drug, saline, acid-alcohol aqueous solvent (required to dissolve buprenorphine at a high concentration), or 3, 30, or 90 mg/kg of buprenorphine intravenously. Serial arterial blood gases were obtained over 3 h. The LD₅₀ determined in triplicate was 146.5 mg/kg (median of 3 series, range: 142.6–176.5). The mean dose received by surviving animals was 96.9 ± 46.7 mg/kg. There was a significant effect of the acid-alcohol aqueous solvent on arterial blood gases. Excluding the solvent effect, 3, 30, and 90-mg/kg buprenorphine doses had no significant effects on arterial blood gases. The toxicity of intravenous buprenorphine in adult rats, assessed by the LD₅₀, is low. These data are consistent with a wide margin of safety of buprenorphine. We determined the median lethal dose of buprenorphine remains to be determined.

Key Words: buprenorphine; acute toxicity; safety; rats; LD₅₀; arterial blood gas; opioids; heroin substitution; drug abuse.

Heroin addiction remains a major concern throughout the world, and the number of opiate overdose deaths, though difficult to assess, appears to have risen in a number of countries over the past decade (Battista et al., 1993; Darke and Zador, 1996; Donoghoe and Hall, 1998; Hall and Darke, 1998; Hammersley et al., 1995; Janssen et al., 1989; Risser and Schneider, 1994; Steentoft et al., 1989, 1996). The approach to treatment of heroin addiction has undergone a profound evolution with the development of substitution treatments, which, in general, involve the utilization of morphinomimetic products (Donoghoe and Hall, 1998). The most commonly prescribed agents are methadone and buprenorphine. High-dose (8–16 mg/day) buprenorphine became available in France in 1996. Buprenorphine is a semisynthetic, highly lipophilic opioid derived from thebaine. Regarding its analgesic properties, buprenorphine is 25 to 50 times more potent than morphine (Reisine and Pasternak, 1996). Buprenorphine acts as an agonist-antagonist for certain morphine receptors. It expresses agonist properties on μ-receptors and antagonist properties on κ-receptors, and has a high affinity for both types of receptors. (Villiger, 1984; Villiger and Taylor, 1981; Wood, 1982) Buprenorphine shows a very slow dissociation from opiate receptors, and consequently, exerts a long activity. Buprenorphine is weakly antagonized by naloxone (Gal, 1989).

Numerous opioids, natural and synthetic, exhibit potent depressant effects on respiration (Reisine and Pasternak, 1996). In contrast, dose-effect relationships of buprenorphine, both in animals and humans, suggest a plateau of respiratory effects (Cowan et al., 1977; Walsh et al., 1994) or no effect at all (Ohtani et al., 1997). The plateau effect of buprenorphine appears of utmost importance regarding its safety for use in substitution treatment.

Deaths have been reported during substitution with both methadone (Battista et al., 1993; Steentoft et al., 1996; Hall and Darke, 1998) and high dose buprenorphine (Brener et al., 1998; Reynaud et al., 1998; Tracqui et al., 1998). Autopsy findings suggest that deaths may be related to respiratory depression (Tracqui et al., 1998). The circumstances and mechanisms of respiratory depression are not well understood. Deaths may result from either misuse or overdose with substitution treatment (Robinson et al., 1993; Tracqui et al., 1998). However, recent reports have emphasized the combination of substitution products (methadone or buprenorphine) with psychotropic drugs (including alcohol and benzodiazepines) as a major factor in fatalities among heroin addicts (Drummer et al., 1993; Hammersley et al., 1995; Tracqui et al., 1998).
The respiratory effects of buprenorphine have been investigated in rats for intra-arterial doses up to 10 mg/kg within a 15-min period after injection (Cowan et al. 1977). However, the respiratory effect was only assessed up to 15 min after injection. Effects of a 3-mg/kg dose were assessed over 8 h after intravenous administration (Ohtani et al. 1997). However, this range of studied doses is far from the previously reported LD₅₀ in rats of more than 30 mg/kg by the intravenous route (Cowan et al., 1977).

The respiratory effects of morphinomimetic drugs can be assessed by parameters such as respiratory rate or minute ventilation. However, respiratory depression is basically defined by alteration of arterial blood gases. To address the acute toxicity and the safety of a single high dose of buprenorphine, we performed the following study. First, we determined the LD₅₀ of intravenous buprenorphine in adult rats. We then studied the effects of buprenorphine 3, 30, and 90 mg/kg on arterial blood gases in adult rats.

**MATERIALS AND METHODS**

All experiments were carried out within the ethical guidelines established by the National Institutes of Health and the French Minister of Agriculture.

**Animals.** Animals employed were Sprague-Dawley male rats (Iffa-Credo, France) weighing between 200 and 300 g at the time of experimentation. They were housed during 8 days before experimentation in a temperature- and light-controlled animal care unit. They were allowed food and water ad libitum until one day prior to experimentation.

**Drugs.** Buprenorphine was generously supplied by Schering-Plough, SA. It was subsequently diluted in a mixture of sterile water (9.4 ml), absolute ethanol (800 μl), and hydrochloric acid 0.1 N (600 μl) at a pH of 4.0, at a concentration of 18.5 mg/ml, the greatest concentration achievable without further lowering the pH. This mixture is referred to throughout this paper as aqueous solvent.

**Study 1: Median Lethal Dose (LD₅₀) of Intravenous Buprenorphine in Rats**

Approximately 18 h prior to experimentation, the animals were fasted, but allowed free access to water. Following drug administration, animals were placed in individual cages, allowed to eat and drink, and maintained in the laboratory, which was temperature-controlled with day lighting. Every effort was made to reduce the number of animals required for the study. Accordingly, the up-and-down method, as proposed by Dixon (Dixon 1991; Dixon and Mood 1948) and refined by Bruce (1985, 1987), was employed. As the Bruce modification of the up-and-down method of LD₅₀ determination was described for use in oral dosing protocols, it was considered prudent to determine the intravenous LD₅₀ in 3 series of different starting doses, in order to assure the reproducibility of the method.

The rats were placed individually in horizontal plexiglas cylinders (internal diameter: 65 cm, adjustable length up to 20 cm) (Harvard Apparatus, Inc., Holliston, MA). Buprenorphine was administered in awake, restrained animals, via the tail vein. Animals were examined repeatedly during the first 4-h period after injection, then daily for 7 days, for evidence of drug-related side effects or other illness. At the end of the study period, animals were euthanized using a carbon-dioxide chamber.

The LD₅₀ was determined on the basis of final dose, outcome/dose pattern, and dose interval.

**Study 2: Effects of High Doses of Buprenorphine on Arterial Blood Gases**

**Anesthesia.** The day before the study, the animals were anesthetized with ketamine (Ketalar®) 70 mg/kg and xylazine (Rompun®) 10 mg/kg intraperitoneally, then placed on a warming blanket with a regulating thermostat. A rectal probe permitted feedback control of the temperature. The stability of anesthesia was judged by complete immobility, deep sleep, and lack of response to painful stimuli.

**Catheterization.** The femoral vein and artery were catheterized with silastic tubing: external diameters ranging from 0.94 to 0.51 mm, respectively; length 30 cm (Dow Corning Co, Midland, MI). The arterial and venous catheters were then tunneled subcutaneously and fixed at the back of the neck. Heparinized saline was injected into each catheter to avoid thrombosis and catheter obstruction. Then, the rats were returned to their individual cages for a minimum 24-h recovery period, to allow for complete washout of the anesthesia. On the day of the experiment, rats were placed in a restraining cage. Before drug injection, the catheters were exteriorized, purged, and their permeability confirmed. No major problems were encountered during catheterization, drug administration, or collection of arterial blood samples.

**Restraint.** The rats were placed individually in horizontal, plexiglas cylinders (internal diameter: 65 cm, adjustable length up to 20 cm) (Harvard Apparatus). The plexiglas cylinders were provided with 4 openings on the cranial extremity and 2 longitudinal openings in the ventral and dorsal faces. Additionally, we placed several holes at the cranial end of the cylinders in order to prevent CO₂ rebreathing.

**Drug administration and collection of arterial blood gases.** The venous catheter permitted the administration of the study drug (no drug, saline, aqueous solvent, or buprenorphine). The arterial catheter permitted blood collection for arterial blood gases. The total volume of 1.2 ml was administered intravenously over 3 min by an infusion pump at a constant rate (Harvard Instruments-PHD 2000, U.S.). For the measurement of the arterial blood gases, blood samples of 300 μl were collected in a heparinized syringe from the arterial catheter. Arterial blood samples were collected before and after injection. Blood samples were collected between 5, 20, 60, 90, 120, and 180 min after the injection of the study drug, and immediately measured by means of a blood-gas analyzer (Radiometer ABL 300, Copenhagen, Denmark).

**Study 2a.** In order to assess the effects of the rapid intravenous administration (3 min) of a 1.2 ml volume, and the effects of the aqueous solvent, 3 groups of 10 restrained animals were studied. The no-drug group received no injection. The saline group received 1.2 ml of physiological saline over 3 min. The solvent group received 1.2 ml of the aqueous solvent over 3 min, and the effects of the aqueous solvent group were compared with those of the no-drug and saline groups.

**Study 2b.** Three groups of 10 restrained animals received 3, 30, or 90 mg/kg of buprenorphine. A constant volume of 1.2 ml was used throughout the study. The effects of the various doses of buprenorphine were compared among the 3 dose groups, and to those induced by the administration of the aqueous solvent alone.

At the end of experiments, rats were euthanized by the injection of a lethal dose of sodium pentobarbital.

**Statistical analysis.** The results are expressed as mean ± SEM. Baseline values were compared using 1-way analysis of variance followed by multiple comparison tests using the Bonferroni correction. In each group the effect of time on arterial blood gases was studied using repeated-measures ANOVA and Dunnett’s multiple comparison tests.

Then, for each sampling time and each drug, we calculated the difference between the value at that time and its corresponding baseline value. These differences were compared using 1-way analysis of variance, followed by multiple comparison tests using the Bonferroni correction. All tests were performed using Prism version 2.0 (GraphPad Software, Inc., San Diego, CA), were 2-tailed, and p values of less than 0.05 were considered significant.
pH, PaCO₂, and PaO₂ did not differ significantly between the groups.

The mean baseline values of arterial blood gases are shown in Table 1. The pH values were within the normal range (7.38 ± 0.05), the PaCO₂ values were significantly lower than in the aqueous solvent group (p < 0.05), and the PaO₂ values were slightly but significantly lower than the baseline values.

In the saline group, there were no significant effects of time on arterial pH. The PaCO₂ values were slightly greater than the baseline value at 20 min, and 120 min (p < 0.05). The PaO₂ values were significantly lower than in the no-drug group at 5 min (p < 0.01), and 20 min (p < 0.05). There was no significant effect on the blood bicarbonate concentrations in comparison with the baseline value. The PaO₂ values were slightly but significantly lower than the baseline values at 5, 20, 60, 90, and 120 min (p < 0.05).

Study 2: Effects of High Doses of Buprenorphine on Arterial Blood Gases

Study 2a: Comparison of the effects of no drug, saline, and aqueous solvent (Fig. 2). The mean baseline values of arterial pH, PaCO₂, and PaO₂ did not differ significantly between the no-drug, saline, and aqueous-solvent groups. Although the mean bicarbonate concentration in the no drug group was significantly lower than in the aqueous solvent group (p < 0.05), the values in the three groups were within the normal range.

Effects of time in each group. In the no-drug group, there were no significant effects of time on arterial pH, PaCO₂, or the bicarbonate concentrations in comparison with the baseline values. The PaO₂ was significantly lower at 20 min (p < 0.05), but remained within the normal range (11.2 ± 0.3 kPa).

In the saline group, there were no significant effects of time on arterial pH. The PaCO₂ values were slightly but significantly greater than the baseline value at 5, 20, 60, and 120 min (p < 0.05). The bicarbonate concentrations and the PaO₂ did not differ significantly from the baseline values.

In the aqueous-solvent group, the arterial pH was significantly lower in comparison with the baseline value at 5, 20, and 120 min (p < 0.05). The PaCO₂ values were significantly greater than the baseline value at 60 and 120 min (p < 0.05). There was no significant effect on the blood bicarbonate concentrations in comparison with the baseline value. The PaO₂ values were slightly but significantly lower than the baseline values at 5, 20, 60, 90, and 120 min (p < 0.05).

Effects of treatment at each sampling time. The arterial pH in the aqueous solvent group was significantly lower than that in the no-drug and saline groups at 5 min (p < 0.01), 20 min (p < 0.01), and 120 min (p < 0.05) (Fig. 2). The lowest pH values were observed in the aqueous-solvent group at 20 (7.38 ± 0.02), and 120 min (7.38 ± 0.01). The PaCO₂ did not differ among the 3 treatment groups at any sampling time. The highest PaCO₂ value was observed in the aqueous-solvent group at 120 min (6.27 ± 0.18 kPa). The bicarbonate concentration in the aqueous-solvent group was significantly greater than in the no-drug group at 90 min (p < 0.01) (Fig. 2). The lowest bicarbonate concentration was observed in the no-drug group at 90 min (23.7 ± 1.0 mmol/l). The PaO₂ did not differ among the 3 treatment groups at any sampling time. The lowest PaO₂ value was observed in the aqueous solvent group at 60 min (9.23 ± 0.63 kPa).

Study 2b: Effects of a single intravenous dose of buprenorphine (Fig. 3). Due to the significant effects of the aqueous solvent on arterial blood gases, the effects of single doses of buprenorphine were compared to those of the aqueous solvent.

Clinical findings. In the rats receiving 3 or 30 mg/kg buprenorphine, we did not observe coma, seizure, ataxia, or obvious abnormal behavior. In the rats receiving 90-mg/kg buprenorphine, we observed only a mild and transient decrease in motor activity within 15 min post-injection. Obvious apnea was noted in any group. It should be noted that there were no deaths in animals having received buprenorphine at 3, 30, or 90 mg/kg.

Baseline values before treatment. There were no significant differences when comparing the baseline values of arterial pH, PaCO₂, PaO₂, or blood bicarbonate concentrations before treatment among the aqueous solvent, 3-, 30-, and 90-mg/kg buprenorphine groups.

Effects of time in each group. In the 3-mg/kg group, the arterial pH was significantly lower than the baseline values at
The PaCO\textsubscript{2} was significantly greater than the baseline values at 5 and 20 min ($p < 0.05$). The blood bicarbonate concentration was slightly but significantly greater than the baseline value at 5 min ($p < 0.05$). The PaO\textsubscript{2} was significantly lower than the baseline values at 5, 20, and 60 min ($p < 0.01$).

In the 30-mg/kg group, the arterial pH was significantly lower than the baseline values at all times ($p < 0.05$). There was a trend towards an increase in the PaCO\textsubscript{2}. However, the differences from the baseline value were not significant at any time. The bicarbonate concentrations were slightly but significantly lower than the baseline values at 120 and 180 min ($p < 0.05$). The PaO\textsubscript{2} was significantly lower than the baseline values at 5, 20, and 60 min ($p < 0.01$).

In the 90-mg/kg group, the arterial pH was significantly lower than the baseline value at only 180 min ($p < 0.05$). There was a trend towards an increase in the PaCO\textsubscript{2}. However, the differences from the baseline value were not significant at any time. The bicarbonate concentrations were not significantly different from the baseline value at any time. The PaO\textsubscript{2} was significantly lower than the baseline values at 5, 20, and 60 min ($p < 0.05$).

**Effects of treatment at each sampling time.** There were no significant differences when comparing the arterial pH, PaCO\textsubscript{2}, and PaO\textsubscript{2} of the aqueous solvent group and the 3-, 30-, and 90-mg/kg buprenorphine groups at any sampling time (Fig. 3). The lowest pH value was observed in the 90-mg/kg buprenorphine group at 180 min (7.32 ± 0.03). The highest PaCO\textsubscript{2} value was observed in the 90-mg/kg-buprenorphine group at 60 min (7.20 ± 0.66 kPa). The lowest PaO\textsubscript{2} value was observed in the 30-mg/kg-buprenorphine group at 20 min (8.47 ± 0.38 kPa). The bicarbonate concentration in the aqueous solvent group was significantly lower than that of only the 3-mg/kg-buprenorphine group, and then only at 5 min ($p < 0.01$) (Fig. 3). The lowest bicarbonate concentration was observed in the 90-mg/kg buprenorphine group at 90 min (25.7 ± 1.2 mmol/l).

**DISCUSSION**

In legitimate substitution treatment, buprenorphine is administered sublingually. However, there is now considerable evidence that buprenorphine is frequently misused and administered by the intravenous route. Indeed, a 12-month survey performed in opiate users presenting to a treatment center in
New Zealand showed considerable intravenous misuse of buprenorphine 0.2 mg tablets, with self-report of misuse in 81% of the patients over the 4 weeks prior to presentation (Robinson et al., 1993). Similarly, Tracqui et al. found misuse in a series of 20 fatalities and 29 cases of acute non-lethal poisoning with high dosage buprenorphine (Tracqui et al., 1998). In 10 non-fatal poisonings, the intravenous route was used. Among the 20 fatalities, 8 showed cutaneous lesions suggestive of IV administration. A syringe was found near the victim in 5 cases. In a population of 53 incarcerated heroin abusers using buprenorphine, 34% reported intravenous administration (Claudon-Charpentier et al., 2000). Thus, we chose to study the acute toxicity of buprenorphine and its effects on arterial blood gases by the intravenous route.

Buprenorphine alone, in this study composed of 3 independent series of animals, has a higher median lethal dose after intravenous injection than has been previously determined. Cowan et al. reported LD₅₀ for buprenorphine administered intravenously to rats weighing only 60–80 g of 38 and 31 mg/kg in male and female rats, respectively. As in our study, the LD₅₀ was assessed over a 7-day period of time (Cowan et al., 1977). It should be noted that Cowan et al. used very young rats for their LD₅₀ study, and thus, our results are not strictly comparable. Our study, performed on adult rats, seems appropriate, given that buprenorphine is most frequently abused by adult humans. However, our study was limited to male rats. Previously, studies dealing with the respiratory effects of opioids also used male rats (Cowan et al., 1977; McCormick et al., 1984; Ohtani et al., 1997). For consistency of our results and in order to allow comparisons with these studies, we chose to study the acute toxicity and respiratory effects of buprenorphine using adult male rats. Thus, the effects of single high doses of buprenorphine in female rats remain to be determined.

Our study underscores the importance of considering the effects of solvents when evaluating the toxicity of a compound requiring the administration of a large volume relative to animal size. In their study of the acute toxicity of buprenorphine in rats, Cowan et al. diluted buprenorphine hydrochloride in saline (Cowan et al., 1977) while Ohtani et al. did not specify the solvent they used (Ohtani et al., 1997). We were unable to dissolve buprenorphine in saline, even at low concentrations. Given the poor water-solubility of buprenorphine and the wide range of doses required to assess the acute toxicity of buprenorphine in adult rats, the use of a non-saline solvent appeared necessary. In comparison with the no drug or saline group, the aqueous solvent induced sustained effects on the arterial blood gases. The arterial pH in the aqueous solvent group was significantly lower than that in the no drug and saline groups. The arterial pH in the aqueous solvent group was significantly lower than that in the no drug and saline groups. The arterial pH in the aqueous solvent group was significantly lower than that in the no drug and saline groups. The arterial pH in the aqueous solvent group was significantly lower than that in the no drug and saline groups.
saline groups at 5, 20, and 120 min, while the \( \text{PaCO}_2 \) did not differ at any sampling time. The decrease in the pH was associated with a concomitant and significant decrease in the blood bicarbonate concentration compared to those in the no-drug group. These data outline the necessity to take into account the effect of the aqueous solvent when studying the respiratory effects of high doses of buprenorphine in rats.

Opioids, both natural and synthetic, have been shown to induce respiratory acidosis and hypoxia. In conscious rats, morphine (0.30–30 mg/kg intra-arterially) increased arterial \( \text{PaCO}_2 \) and reduced \( \text{PaO}_2 \). The response to morphine increased linearly with dose and showed no signs of recovery at 45 min. (Cowan et al., 1977). Acute administration of methadone (5-mg/kg ip) caused a significant decrease in arterial pH and \( \text{PaO}_2 \) and an increase in \( \text{PaCO}_2 \) in rats (McCormick et al., 1984). Data obtained in animals following a single dose of buprenorphine, with regard to both the respiratory rate and the arterial blood gases, are consistent with either a plateau effect (Cowan et al., 1977) or no effect at all (Ohtani et al., 1997). In mice, buprenorphine administered subcutaneously in the range of 0.001–10 mg/kg caused a reduction of the respiratory rate, the maximum effect occurring after 0.10 mg/kg, when a 22% reduction was recorded (Cowan et al., 1977). In rats, buprenorphine (0.01–10 mg/kg intra-arterially) increased arterial \( \text{PaCO}_2 \) and reduced \( \text{PaO}_2 \) at 15 min. The dose-effect relationship showed that depression of respiration reached a plateau over the dose-range 0.10–10 mg/kg. Interestingly, the duration of respiratory depression became less as the dose of buprenorphine was increased. Thus, after 10 mg/kg, the \( \text{PaCO}_2 \) and \( \text{PaO}_2 \) had returned to control values at 45 min (Cowan et al., 1977). Ohtani et al. studied the respiratory effects of an iv bolus of buprenorphine in the range of 0.008 to 3 mg/kg in rats. Neither the respiratory rate nor the arterial \( \text{PaCO}_2 \) level changed over the dose range studied (Ohtani et al., 1997). During the continuous intravenous infusion of buprenorphine in rats (20 mg/kg/h), the respiratory rate gradually decreased, with a minimum respiratory rate being observed 3 h after the beginning of infusion. However, the decrease was not statistically significant, even at the highest infusion rate (Ohtani et al., 1997). In healthy adult volunteers, the clinical pharmacology and safety profile of buprenorphine was assessed with doses ranging from 1 to 32 mg administered sublingually (Walsh et al., 1994). Respiratory rate was significantly depressed after buprenorphine administration and oxygen saturation was decreased (Walsh et al., 1994). Buprenorphine maximally reduced respiratory rate by 4 breaths per min at doses of 4 mg and higher, and oxygen saturation was reduced from 98% during placebo conditions to a minimum of 95 to 96% after the 8-, 16-, and 32-mg doses. This study showed the existence of a ceiling on some respiratory effects of buprenorphine in humans (Walsh et al., 1994).

In our study, it should be noted that the LD\(_{50}\) was determined using the bolus administration of buprenorphine by a tail vein, while the study of the effects on arterial blood gases used the intravenous administration of buprenorphine over a 3-min period via an indwelling catheter. We chose to administer the drug in the arterial blood-gas studies not as an intravenous bolus but rather as a rapid intravenous infusion, in order to prevent any effect of fluid overload on arterial blood gases. We did not observe any significant effect of the 3, 30, or 90 mg/kg doses of buprenorphine, distinct from the effect of the aqueous solvent. In contrast to the lack of effects on arterial blood gases in this study, 90 mg/kg approaches the minimum lethal dose (120 mg/kg) found in our LD\(_{50}\) study. Nonetheless, we cannot exclude that a dose greater than 90 mg/kg would have resulted in respiratory depression. However, our data are consistent with a limited effect of a single intravenous dose of buprenorphine up to 90 mg/kg on respiration, as assessed by arterial blood gases. Since buprenorphine is a commonly used analgesic in rats and other animals, the information generated from this study should also be of veterinary interest. However, the safety of single high doses of buprenorphine was assessed in only one rodent species. It should be outlined that the mechanism of death induced by a lethal dose of buprenorphine to rats remains to be determined.

The mechanisms of the previously reported respiratory effects of buprenorphine are complex. Some data suggest that buprenorphine-induced respiratory depression is related to norbuprenorphine, the active metabolite of buprenorphine (Ohtani et al., 1997). Norbuprenorphine, a weak analgesic, is a potent respiratory depressant in rats (Ohtani et al., 1995). The respiratory-depressant activity of norbuprenorphine appears to be approximately 10 times more potent than that of buprenorphine (Ohtani et al., 1997). If one assumes that norbuprenorphine is in fact responsible for respiratory depression after buprenorphine administration, our data would suggest that, even at a dose of 90 mg/kg, acute formation of norbuprenorphine is likely very limited. This may be a greater problem with chronic buprenorphine use.

In conclusion, the LD\(_{50}\) of intravenous buprenorphine in adult rats was 146.5 mg/kg. Our data showed a lack of significant effects of buprenorphine on arterial blood gases in adult rats. These data are consistent with a wide margin of safety for buprenorphine. The mechanism of death after the intravenous administration of a single lethal dose of buprenorphine remains to be determined.

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