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Respiratory effects of buprenorphine/naloxone alone and in combination with diazepam in naive and tolerant rats

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HIGHLIGHTS

- Like buprenorphine alone, buprenorphine/naloxone does not depress ventilation in rats.
- IV buprenorphine/naloxone injection induces withdrawal symptoms in tolerant rats.
- Naloxone does not prevent the deleterious respiratory effects of buprenorphine/diazepam.

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ABSTRACT

Respiratory depression has been attributed to buprenorphine (BUP) misuse or combination with benzodiazepines. BUP/naloxone (NLX) has been marketed as maintenance treatment, aiming at preventing opiate addicts from self-injecting crushed pills. However, to date, BUP/NLX benefits in comparison to BUP alone remain debated. We investigated the plethysmography effects of BUP/NLX in comparison to BUP/solvent administered by intravenous route in naive and BUP-tolerant Sprague-Dawley rats, and in combination with diazepam (DZP) or its solvent. In naive rats, BUP/NLX in comparison to BUP significantly increased respiratory frequency (f, $P<0.05$) without altering minute volume (V_E). In combination to DZP, BUP/NLX significantly increased expiratory time ($P<0.01$) and decreased f ($P<0.01$), tidal volume (V_T, $P<0.001$), and V_E ($P<0.001$) while BUP only decreased V_T ($P<0.5$). In BUP-tolerant rats, no significant differences in respiratory effects were observed between BUP/NLX and BUP. In contrast, in combination to DZP, BUP/NLX did not significantly alter the plethysmography parameters, while BUP increased inspiratory time ($P<0.001$) and decreased f ($P<0.01$) and V_E ($P<0.001$). In conclusion, differences in respiratory effects between BUP/NLX and BUP are only significant in combination with DZP, with increased depression in naive rats but reduced depression in BUP-tolerant rats. However, BUP/NLX benefits in humans remain to be determined.

1. Introduction

Buprenorphine (BUP), a semi-synthetic opioid, is widely used as effective maintenance treatment in heroin addicts. In humans (Yassen et al., 2007) as well as rodents (Chevillard et al., 2009), BUP exhibits ceiling respiratory effects in contrast to other opioids, supporting its safety profile. However, following its marketing, asphyxic fatalities (Häkkinen et al., 2012) and poisonings with typical opioid features and respiratory depression (Mégarbane et al., 2010) were attributed to BUP misuse or concomitant ingestion of benzodiazepines (BZD). Intravenous (iv) BUP misuse among drug

Abbreviations: BUP, buprenorphine; NLX, naloxone; BZD, benzodiazepine; DZP, diazepam; GABA, gamma-aminobutyric acid; FLZ, flumazenil; f, respiratory frequency; V_E, minute volume; V_T, tidal volume; T_E, expiratory time; T_I, inspiratory time; T_{TOT}, respiratory cycle duration; ip, intraperitoneal; iv, intravenous; sc, subcutaneous.

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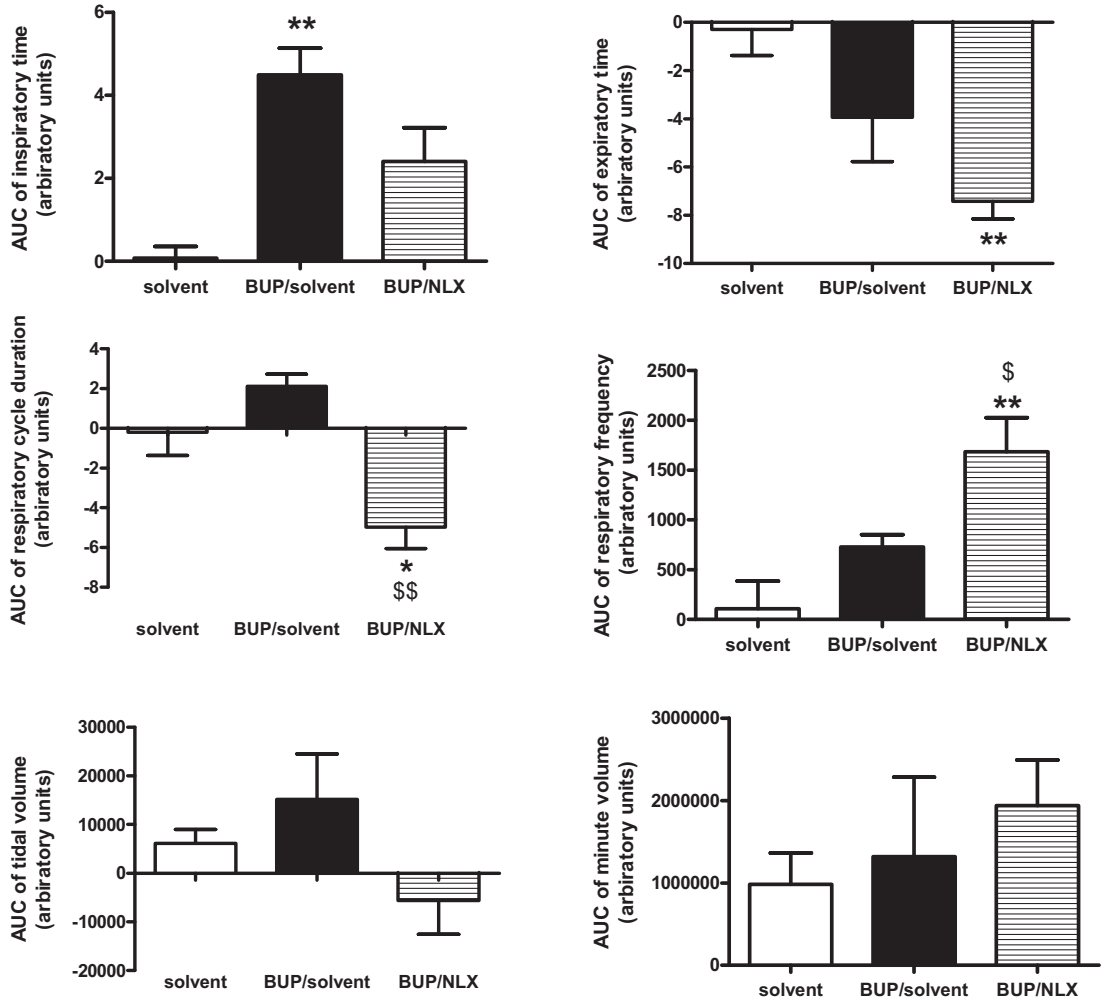

Fig. 1. Plethysmography effects in Sprague-Dawley rats of solvent (white), 30 mg/kg buprenorphine/solvent (BUP/solvent, black), and 30 mg/kg buprenorphine/7.5 mg/kg naloxone (BUP/NLX, horizontal lines). Each group consisted of six rats. Values represent mean ± SEM of the areas under the curve (AUC) of each parameter between the time before intravenous administration and 60 min post-injection. Data are expressed as arbitrary units. Comparisons were performed using ANOVA followed by multiple tests with Bonferroni's correction. BUP/solvent or BUP/NLX vs. solvent: $^{*}P < 0.05$, $^{**}P < 0.01$; BUP/NLX vs. BUP/solvent: $^{\$}P < 0.05$, $^{\$\$}P < 0.01$.

addicts is frequent, mainly to modulate opiate withdrawal symptoms arising from either attempted self-detoxification in case of insufficient funds to purchase preferred illicit opioids or inability to find a preferred source of drugs, and rarely to experience pleasure or euphoria (Monte et al., 2009). Additionally, studies suggested deleterious interactions between BUP and BZD, resulting rather from pharmacodynamic than pharmacokinetic mechanisms (Gueye et al., 2002; Lintzeris and Nielsen, 2010). Interestingly, in BUP-poisoned patients, 0.4–0.8 mg naloxone (NLX), an opioid receptor antagonist, did not reverse neuro-respiratory toxicity whereas flumazenil (FLZ), a gamma-aminobutyric acid (GABA)-A receptor antagonist, did (Mégarbane et al., 2010).

Since 2006, BUP/NLX combination (ratio 4:1) has been marketed, aimed at dissuading iv self-injection of crushed tablets. While sublingual intake of BUP/NLX avoids NLX effects due to its limited bioavailability, iv or intranasal misuse of BUP/NLX is supposed to result in acute withdrawal in opiate abusers described as "bad experience" (Orman and Keating, 2009; Robinson et al., 1993; Simojoki et al., 2008). Switching from BUP to BUP/NLX was effective and well-tolerated (Daulouède et al., 2009; Demetrovics et al., 2009; Simojoki et al., 2008; Stimolo et al., 2010). In addition, a possible reduction in BUP/NLX abuse potential was expected, based on studies reporting withdrawal symptoms in drug addicts misusing this combination (Amass et al., 2012; Degenhardt et al., 2009; Elkader and Sproule, 2005; Fiellin et al., 2001, 2006; Larance et al., 2011; Orman and Keating, 2009; Simojoki et al., 2008; Smirnov and Kemp, 2012; Vicknasingam et al., 2010), even though such symptoms were not reported in all studies (Comer et al., 2010; Harris et al., 2000; Mendelson and Jones, 2003; Robinson et al., 1993). However, since its marketing, there has been no significant reduction in BUP/NLX misuse in either dependent (Bazazi et al., 2011; Bruce et al., 2009; Larance et al., 2011; Monte et al., 2009; Uosukainen et al., 2013) or non-dependant opioid abusers (Comer and Collins, 2002; Duke et al., 2010; Strain et al., 2000) and injection-related risk behaviors like syringe sharing (Bruce et al., 2009). Similarly to BUP, fatalities and overdoses with respiratory depression have been attributed to BUP/NLX (Häkkinen et al., 2013; Pedapati and Bateman, 2011). Surprisingly, significant increase in BZD use has also been reported among drug addicts following BUP/NLX marketing (Bruce et al., 2009; Vicknasingam et al., 2010). Concerns regarding interactions between BUP/NLX and BZD have been also raised with reported life-threatening cases of respiratory depression (Martin, 2011; Rich et al., 2011).

To date, no study has assessed BUP/NLX-induced respiratory effects and the resulting interactions with BZD. We designed an experimental study in naive and BUP-tolerant rats to investigate BUP/NLX-induced respiratory effects administered alone or in