Influence of Ethanol on Oxycodone-induced Respiratory Depression

A Dose-escalating Study in Young and Elderly Individuals

Rutger van der Schrier, M.D., Margot Roozekrans, M.D., Erik Olofsen, M.Sc., Leon Aarts, M.D., Ph.D., Monique van Velzen, Ph.D., Merijn de Jong, B.Sc., Albert Dahan, M.D., Ph.D., Marieke Niesters, M.D., Ph.D.

ABSTRACT

Background: Respiratory depression is a potentially fatal complication of opioid use, which may be exacerbated by simultaneous ethanol intake. In this three-way sequential crossover dose-escalating study, the influence of coadministration of oral oxycodone and intravenous ethanol was assessed on resting ventilation, apneic events and the hypercapnic ventilatory response in healthy young and older volunteers.

Methods: Twelve young (21 to 28 yr) and 12 elderly (66 to 77 yr) opioid-naive participants ingested one 20 mg oxycodone tablet combined with an intravenous infusion of 0, 0.5, or 1 g/l ethanol. Resting respiratory variables and the primary outcome, minute ventilation at isohypercapnia (end-tidal partial pressure of carbon dioxide of 55 mmHg or VE55), were obtained at regular intervals during treatment.

Results: Oxycodone reduced baseline minute ventilation by 28% ($P < 0.001$ *vs.* control). Ethanol caused a further decrease of oxycodone-induced respiratory depression by another 19% at 1 g/l ethanol plus oxycodone ($P < 0.01$ *vs.* oxycodone). Ethanol combined with oxycodone caused a significant increase in the number of apneic events measured in a 6-min window with a median (range) increase from 1 (0 to 3) at 0 g/l ethanol to 1 (0 to 11) at 1 g/l ethanol ($P < 0.01$). Mean (95% CI) VE55 decreased from 33.4 (27.9 to 39.0) l/min (control) to 18.6 (15.6 to 21.6) l/min (oxycodone, $P < 0.01$ *vs.* control) and to 15.7 (12.7 to 18.6) l/min (oxycodone combined with ethanol, 1 g/l; $P < 0.01$ *vs.* oxycodone).

Conclusions: Ethanol together with oxycodone causes greater ventilatory depression than either alone, the magnitude of which is clinically relevant. Elderly participants were more affected than younger volunteers. **(ANESTHESIOLOGY 2017; 126:534-42)**

OPIOIDS produce potentially life-threatening respiratory depression through their action at μ-opioid receptors present in brainstem respiratory centers.[1,2] Numerous studies have shown that exogenous opioids decrease the ventilatory responses to hypercapnia and hypoxia, cause irregular breathing and at high dose cause the complete cessation of rhythmic respiratory activity.[1,2] Recent studies indicate that a large number of visits to the emergency department are because of abuse or misuse of legally prescribed opioids (*e.g.*, the use of higher doses than prescribed, the use of prescription opioids in sometimes opioid-naive individuals who are not pain patients) that involved concomitant ethanol consumption.[3,4] Additionally, data from the forensic literature indicate that the combined use of opioids and ethanol is a frequent observation in postmortem blood analysis.[5,6] These data suggest a possibly contributing role of ethanol in the deleterious respiratory effects of (prescription) opioids, possibly due to the enhancement of sedation.[7]

What We Already Know about This Topic

- Many visit the emergency department because of misuse or abuse of legally prescribed opioids that involve concomitant ethanol consumption, suggesting that opioid-induced respiratory depression may be exacerbated by simultaneous ethanol intake

What This Article Tells Us That Is New

- Oxycodone (oral 20 mg immediate release) significantly reduced baseline minute ventilation, the slope of the hypercapnic ventilatory response curve, and minute ventilation at an end-tidal partial pressure of carbon dioxide of 55 mmHg in healthy young and elderly opioid-naive volunteers
- Baseline minute ventilation and minute ventilation at an end-tidal partial pressure of carbon dioxide of 55 mmHg were further impaired by the concomitant administration of ethanol, independent of dose
- Elderly subjects were especially likely to have repeated apneic events produced by the ethanol–oxycodone combination, resulting in frequent episodes of oxygen desaturation

Ethanol is a legal substance that affects various physiologic processes including arousal, cognition, and motor skills.[7,8]

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Ethanol has a predominant depressant effect on the central nervous system due to enhancement of γ-aminobutyric acid–mediated and reduction of glutamatergic neuronal transmission.[9,10] Since these receptor systems play an important role in the generation of respiratory activity,[11,12] it is expected that the combination of opioids and ethanol potentiates respiratory depression. Somewhat surprisingly, just few studies addressed the effect of ethanol and its combination with opioids on breathing. Setnik *et al.*[13] observed a decrease in end-tidal carbon dioxide concentration when 0.7 g/l ethanol was administered on top of 80 mg oral morphine. This suggests a stimulatory effect of ethanol on opioid-induced respiratory depression (OIRD). Studies on the effect of just ethanol are equivocal with respect to its effect on breathing with studies showing a small stimulatory effect,[14–17] no effect,[18] or a depressant effect.[19,20] We relate these divergent outcomes to differences in doses, study methods, and populations tested.

In the current proof-of-concept study, we examined the effect of ethanol (0, 0.5, and 1 g/l) on OIRD induced by 20 mg oral oxycodone. We studied healthy and opioid-naive young adult and elderly volunteers. The main endpoint of our study was ventilation at an end-tidal partial pressure of carbon dioxide of 55 mmHg derived from the steady-state ventilatory response to hypercapnia. Our study is a first to study relatively high opioid and ethanol doses in opioid-naive elderly healthy individuals. Since elderly individuals display an increased sensitivity to opioids and ethanol,[8,21,22] we used a dose-escalating, single-blind design, allowing us to continuously evaluate the safety of participants and make an informed decision on whether to continue to a next cohort in case of specific issues such as low oxygen saturation or long-term apneas. The relatively high opioid dose was chosen to emphasize the magnitude of OIRD, but our approach is not academic as various studies show the presence of relatively high opioid doses on first prescriptions.[23,24] We hypothesize that ethanol enhances OIRD and that particularly the elderly population is at higher risk for respiratory depression when oxycodone is combined with ethanol. In this study, ethanol was measured in the exhaled air.

Materials and Methods

Subjects

This three-way crossover dose-escalating study (within each age cohort) was performed from October 2013 to December 2014. The protocol was approved by the local Institutional Review Board (IRB; Commissie Medische Ethiek, Leiden, The Netherlands) and the Central Committee on Research Involving Human Subjects (CCMO) in The Hague, The Netherlands. Participants were recruited by advertisement in the local newspaper and flyers posted within the facilities of Leiden University (Leiden, The Netherlands). All subjects gave written informed consent before enrollment in the study. After receiving informed consent, the subjects gave their medical history and received a physical examination; then blood chemistry (renal and liver functions) results were obtained. An independent physician who was not part of the research team performed the screening. The study was registered at trialregister.nl under number NTR4123.

Inclusion criteria were the absence of any medical (*e.g.*, current pulmonary, cardiac, renal, or metabolic), neurologic, or psychiatric illness; age 20 to 30 yr (young participants) or 65 yr or older (elderly participants); and a body mass index (BMI) of 18 to 35 kg/m^2. The BMI range was relatively large to obtain a representative sample of individuals in the population. Exclusion criteria were abnormalities on physical examination or blood chemistry, a high risk of obstructive sleep apnea as determined by the STOP-BANG questionnaire (score greater than 4),[25] pregnancy/lactation, weekly ethanol intake of more than 3 units/day or more than 21 units/week, illicit drug use in 3 months before enrollment or a positive urine dip-stick drug test during screening or on the morning of the study (Alere Toxicology Plc., Oxfordshire, United Kingdom; the stick tests for cocaine, amphetamine, cannabinoids, phencyclidine, methadone, benzodiazepines, tricyclic antidepressants, and barbiturates), current use of any medication, and a Mini Mental State Examination less than 28. The latter exclusion criterion was to prevent that subjects with some form of cognitive impairment participated.

Intervention

Subjects received oral oxycodone on three occasions with at least 2 weeks between study days. On all three visits, the subjects received an intravenous ethanol infusion that was initiated before the 20 mg oxycodone immediate release tablet (Mundipharma Pharmaceuticals BV, The Netherlands) intake but after baseline respiratory measurements. Treatments were not assigned randomly. A dose escalation of the ethanol dose was performed from placebo on visit 1 to breath ethanol concentrations of 0.5 g/l on visit 2 and 1.0 g/l on visit 3, as requested by the IRB. Participants and the research nurses were not informed on the order of treatment.

A clamping method was used to achieve the target pseudo-steady-state breath ethanol concentration.[26] The clamping method is based on the fact that after ethanol elimination is fully saturated, the ethanol elimination is constant and independent of concentration. As a result, a change in infusion rate will result in a proportional change in steady-state blood ethanol concentration within 30 min. Each subjects received an intravenous infusion of 10% ethanol w/v in 5% glucose diluted in 0.9% NaCl. Dilution was necessary to prevent infusion site pain from the initially high infusion rates of ethanol. The initial infusion rate was based on the estimated body water as derived from weight, age, and sex. After 10 min, the infusion rates were adapted according to the measured breath ethanol concentration (Alco Sensor IV meter; Honac Nederland BV, The Netherlands). Once the target steady-state measured breath ethanol concentration was reached and after a set of respiratory measurements, the oxycodone tablet was ingested with 100 ml noncarbonated water.

The expired breath ethanol concentration of 0.5 g/l corresponds to 1 unit/h ethanol in women and 3 units/h in men, while 1 g/l corresponds to 3 units/h in women and 5 units/h in men.

Apparatus

Steps in end-tidal pressure of carbon dioxide ($P_{ET}CO_2$) were applied using the *dynamic-end-tidal forcing* technique. The dynamic-end-tidal forcing technique enables changes in $P_{ET}CO_2$ while keeping the end-tidal oxygen concentration constant. The technique is described in detail elsewhere.[27] In brief, subjects breathed through a mask over mouth and nose that was attached to a pneumotachograph/pressure transducer system (#4813; Hans Rudolph Inc., USA) and to a set of mass flow controllers (Bronkhorst High Tech, The Netherlands) for the delivery of oxygen, carbon dioxide, and nitrogen. The mass flow controllers were controlled by a computer running the custom-made RESREG/ACQ software (Leiden University Medical Center, The Netherlands). The software allows for the steering of the end-tidal gas concentrations (by varying the inspired concentration) and the acquisition of respiratory variables. The inspired and expired oxygen and carbon dioxide partial pressures were measured at the mouth using a capnograph (Datex Capnomac, Finland). Heart rate and arterial oxygen saturation measured by pulse oximetry (Spo_2; Masimo Corporation, USA) were measured continuously.

Measurements

Respiratory measurements without inhalation of any inspired carbon dioxide and hypercapnic ventilatory response (HCVR) curves were obtained at four separate periods: before any drug administration, after the measured steady-state breath ethanol concentration was reached, and 60 and 120 min after oxycodone administration. Baseline variables were minute ventilation, respiratory rate, tidal volume, Spo_2. Additionally, the number of apneic events was measured in which an apneic event was defined as the absence of inspiratory flow (as measured by the pneumotachograph) for at least 10 s measured in the 6 min before carbon dioxide inhalation. To obtain the HCVR, four steps in the end-tidal partial pressure of carbon dioxide were applied with step sizes of 4.5 mmHg (0.6 kPa), 9 mmHg (1.2 kPa), 13.5 mmHg (1.8 kPa), and 18.0 mmHg (2.4 kPa) above resting $P_{ET}CO_2$. Each $P_{ET}CO_2$ step lasted 6 to 8 min, assuming at least 2 min of steady-state ventilation. The order of the steps was arbitrarily set. Throughout each HCVR, the end-tidal oxygen partial pressure was maintained at a normoxic level of 105 mmHg (14 kPa). Only in case of desaturations, supplemental inspired oxygen fraction was given (0.5 to 1.0).

Information on subjectively experienced sedation was obtained at baseline and after drug administration. We used a 100-mm visual analogue scale that represents the subjective feeling of alertness/drowsiness and that ranges from 0 (fully alert) to 100 (unable to keep the eyes open).[28]

Safety

Stopping rules were applied when the subject indicated that he or she wanted to discontinue the experiment or in case of an adverse event. Adverse events were defined by loss of respiratory activity for 90 s or longer, despite active stimulation of the subject, end-tidal partial pressure of carbon dioxide greater than 67.5 mmHg, Spo_2 less than 85% for at least 2 min, or any other situation or condition that may have interfered with the health of the participant. Additionally, the investigators were allowed to stimulate the subjects to breathe or give supplemental oxygen in case they felt this was needed to prevent any adverse event. In case of adverse events, continuation into the next cohort was determined in close cooperation with our department's Data Safety and Monitoring Board (Leiden, The Netherlands).

Data and Statistical Analysis

The placebo ethanol infusion before oxycodone intake was defined as the control condition. The study was powered to detect a reduction of the slope of the HCVR by 0.4 $L \cdot min^{-1} \cdot mmHg^{-1}$ (SD 0.4) at the combination of oxycodone and a breath ethanol concentration of 1 g/l *versus* control. Assuming similar variances of the slope before and after treatment, a sample size of 12 per age group would lead to a power greater than 90% to detect these effects at $P < 0.05$. The sample size analysis was performed in SigmaPlot v12.0 (Systat Software Inc., USA). In the event of discontinuation or withdrawal of informed consent, the data were discarded and the participant was replaced. Independent study monitoring was performed. Data analysis was launched after the monitor filed the final report, ensuring that all Good Clinical Practice requirements were met.

The slope of the HCVR was estimated in R (The R Foundation for Statistical Computing, www.r-project.org, accessed January 1, 2017). To that end, data analysis was automated: (1) from the raw data, the medians of the 1-min

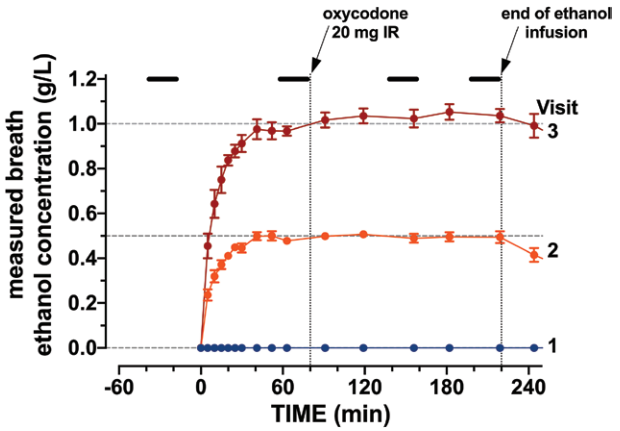

Fig. 1. Measured breath ethanol concentration profiles (mean and 95% CIs) obtained during infusion of 0, 0.5, and 1.0 g/l. At *t* (time) = 0 min, the infusion of ethanol started; at *t* = 80 min, a 20 mg oxycodone immediate release (IR) tablet was ingested. Respiratory measurements are indicated by the *black bars*.

breath-to-breath minute ventilation were calculated; (2) all measurements obtained without carbon dioxide stimulation (baseline ventilation) and measurements during the final 2 min of each hypercapnic step, representing steady-state hypercapnic ventilation, were selected for further analysis; (3) The HCVR data (V_I *vs.* $P_{ET}CO_2$) were fitted to obtain the slope of the HCVR (fig. 1).

To get an indication on the effect of treatment on the variability of breathing, the percentage coefficient of variation (%CV) was calculated for tidal volume and the duration of one breath (inspiratory time plus expiratory time) during the 6 min before carbon dioxide stimulation, without taking the apneic events into account.

Three time points were included in the statistical analysis: control, ethanol infusion (before oxycodone administration), and ethanol combined with oxycodone. For the latter time point, we had two measurements (60 and 120 min after oxycodone intake). We included the data point that displayed the greatest degree of depression of ventilation in the analysis. We did so to take into account the large intersubject variability in oxycodone pharmacokinetics.[29]

Statistical analysis was performed on respiratory variables without carbon dioxide inhalation (ventilation, respiratory rate, tidal volume, $P_{ET}CO_2$, Spo_2, number of apneas, and %CV) and data obtained during carbon dioxide inhalation (HCVR slope and primary endpoint VE55). VE55 is the ventilation at 55 mmHg, which was extrapolated from the HCVR, and takes both the slope and position of the HCVR into account, hence gives a better reflection of the respiratory effect of the intervention.

Data analysis was on the total population, and subgroup analysis was performed (young *vs.* elderly participants) as *a priori* specified. The data were analyzed using a population averaged model with infusion (expired breath ethanol concentration 0, 0.5, and 1 g/l), visit and infusion × visit as fixed factors, subject as a repeated statement and baseline values as covariate. For pairwise comparisons, a Bonferroni correction was applied. A linear mixed model with a Poisson distribution and log link was used to test whether significant differences in the number of apneas were observed among treatment levels. Data analysis was performed using SPSS v23.0 for Windows (IBM Corporation, USA); $P < 0.05$ were considered significant. Data are presented as mean (95% CI) or median (range), unless otherwise stated.

Results

Participants and Adverse Events

Forty (13 young and 27 participants in the older age group) subjects were screened, of whom 14 (1 young and 13 elderly) subjects did not participate for logistic reasons (other commitments on the day of the study) or because they did meet exclusion criteria (BMI greater than 35 kg/m^2, mini-mental state examination less than 28). Twenty-six subjects were treated, of whom one young and one elderly female subjects terminated the study early due to discomfort. Twenty-four participants (12 young and 12 elderly), all Caucasians, completed all three sessions; their characteristics are given in table 1. Mean (range) age of the young participants was 24 (21 to 28) yr and that of the participants in the elderly group was 70 (66 to 77) yr. Mean measured breath ethanol concentrations over time are given in figure 1. An example of the effect of 1 g/l ethanol combined with oxycodone on the HCVR obtained in one elderly participant is given in figure

Table 1. Participants' Characteristics

	Young Participants	Elderly Participants
Sex distribution (M/F)	6/6	6/6
Age, yr	24 ± 2 (21–28)	70 ± 4 (66–77)
Weight, kg	75 ± 11 (59–89)	70 ± 10 (61–81)
Height, cm	181 ± 8 (170–193)	169 ± 8 (162–186)
BMI, kg/m^2	22.9 ± 2.3 (18.6–26.5)	24.4 ± 2.7 (21.7–31.6)
Weekly ethanol intake (all)	10 ± 4 (4–15)	9 ± 7 (2–21)
Weekly ethanol intake, men	11 ± 4 (10–15)	9 ± 7 (2–21)
Weekly ethanol intake, women	10 ± 4 (4–8)	10 ± 8 (2–21)

Values are mean ± SD (range). One unit of ethanol intake equals a consumption of 250 ml of 5% alcohol.

BMI = body mass index; F = female; M = male.

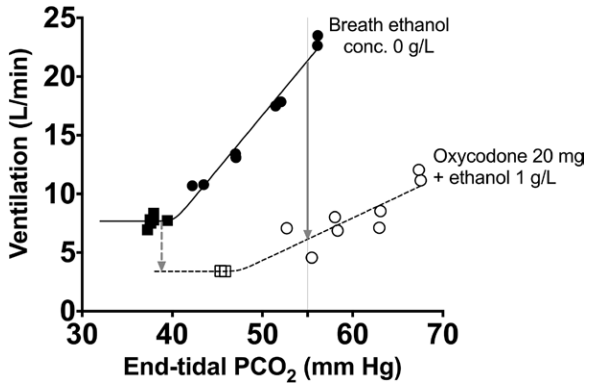

Fig. 2. Ventilatory response to hypercapnia of an elderly participant under placebo conditions (breath ethanol concentration of 0 g/l infusion) and during coadministration of ethanol (breath concentration of 1 g/l) and 20 mg oxycodone immediate release. *Squares* denote resting data points without added inspired carbon dioxide; *circles* denote data obtained at added inspired carbon dioxide. All data points are 1-min median values obtained at steady-state ventilation. The *line* through the data is the data fit. The *horizontal* part of the data fit represents the estimation of resting ventilation, the *linear ramp* is the hypercapnic ventilatory response curve. The continuous *vertical gray line* depicts VE55 or the extrapolated minute ventilation at an end-tidal partial pressure of carbon dioxide (P_{CO_2}) of 55 mmHg; the continuous *gray arrow* is the decline in VE55 due to oxycodone and 1 g/l ethanol. The *broken gray arrow* is the decline in resting ventilation due to oxycodone and 1 g/l ethanol.

2. All young subjects completed the study without any serious adverse effects. Two elderly subjects required supportive care because of Spo_2 levels of less than 80%. They were stimulated to take several deep breaths upon which their oxygen saturation increased to values greater than 90% within 2 min. Hence, their actual decline in oxygen saturation is partly masked by these per-protocol interventions. No other adverse events occurred in the elderly population.

Sedation

Ethanol had no effect on the sedation visual analogue scale (max. score 21 mm on the 100-mm scale; $P > 0.05$ *vs.* control); however, the intake of oxycodone did result in significant sedation (sedation range 45 to 47 mm among treatments; $P < 0.001$ *vs.* control), which was independent of the measured breath ethanol concentration (table 2).

Apnea

Apneic events were observed in 11 (of the 12) young participants (total number of events 68), with more than two events occurring in at least one measurement window in four subjects. In this subpopulation, we counted 42 apneic events of which 8 occurred during the combination of oxycodone and ethanol 1 g/l (table 3; fig. 3). In the elderly group, 11 (of 12) participants had at least one apneic episode (total number of events 120). In nine participants, there were more than two events in at least one of the measurement windows. In this subpopulation, there were 118 apneas, with 54 occurring when oxycodone was combined with ethanol 1 g/l. Comparing the two age groups showed a greater number of apneic events in the older subjects with respect to total events and those occurring during oxycodone plus ethanol 1 g/l ($P = 0.02$, Fisher exact test). In all subjects, apneic events were preceded by irregular breathing (increase in %CV, see the Variability subsection below) and reduced respiratory rates.

Oxygen Saturation, Ventilation, and End-tidal Pco_2

Ethanol infusion alone had just a modest effect on Spo_2 (reduction by 2 and 1% at 0.5 and 1.0 g/l ethanol, respectively; table 2; fig. 4) without affecting any of the other variables. Oxycodone had a significant depressant effect on ventilation. Combining oxycodone with ethanol produced a significant additional increase in respiratory depression, which was reflected by the further decrease in ventilation, with the lowest ventilation observed during the combined treatment of 1 g/l ethanol and oxycodone (mean ventilation 4.7 [4.1 to 5.2] l/min; table 2; fig. 4). At this treatment level, a significant age effect was detected with greater depression of ventilation in the elderly group (young, 5.4 [4.6 to 6.2] l/min *vs.* elderly 4.1 [3.2 to 5.0] l/min; $P = 0.04$). Additional signs of respiratory depression from the ethanol oxycodone combination were the increase in $P_{ET}CO_2$ and reduction in Spo_2, with similar effects at the two ethanol levels (mean increase in $P_{ET}CO_2$ 5, 8, and 8 mmHg and decrease in Spo_2 by 5, 8, and 8% at breath ethanol concentrations of 0, 0.5, and 1 g/l, respectively; table 2; fig. 4).

Table 2. Influence of Ethanol at Target Breath Concentrations of 0, 0.5, and 1 g/l, 20 mg oxycodone, and Their Combination on Respiratory Variables and Sedation Score

Alcohol Concentration	Baseline	Ethanol Infusion	20 mg Oxycodone Plus Ethanol Infusion
Number of apneic events lasting > 10 s			
0 g/l	0 (0–5)	0 (0–5)	1 (0–3)*
0.5 g/l	0 (0–4)	0 (0–5)	1 (0–8)†
1.0 g/l	0 (0–5)	0 (0–3)	1 (0–11)†
Ventilation, l/min			
0 g/l	8.0 (7.4–8.5)	8.0 (7.5–8.5)	5.8 (5.4–6.2)‡
0.5 g/l	8.2 (7.5–8.9)	7.5 (6.9–8.1)	5.1 (4.4–5.7)
1.0 g/l	8.1 (7.6–8.6)	8.0 (7.5–8.5)	4.7 (4.1–5.4)†
Tidal volume, ml			
0 g/l	734 (641–827)	684 (611–757)	529 (469–590)‡
0.5 g/l	722 (619–825)	638 (573–702)	504 (455–552)
1.0 g/l	691 (602–780)	642 (562–722)	468 (408–527)
Respiratory rate, min^{-1}			
0 g/l	12 (10–13)	13 (11–14)	11 (10–11)*
0.5 g/l	12 (11–13)	12 (11.3–14)	10 (9–11)
1.0 g/l	13 (11–14)	13 (11–14)	9 (8–10)
End-tidal Pco_2, mmHg			
0 g/l	37 (35–38)	37 (35–38)	41 (39–44)‡
0.5 g/l	36 (35–38)	37 (35–38)	44 (42–45)†
1.0 g/l	37 (35–38)	36 (34–38)	44 (42–46)†
Oxygen saturation, %			
0 g/l	98 (98–99)	98 (97–99)	94 (92–95)‡
0.5 g/l	98 (97–99)	96 (96–97)‡	90 (87–92)†
1.0 g/l	98 (97–98)	97 (96–98)‡	89 (86–93)†
Slope of the HCVR, $l \cdot min^{-1} \cdot mmHg^{-1}$			
0 g/l	2.0 (1.7–2.3)	2.0 (1.6–2.4)	1.4 (1.2–1.6)*
0.5 g/l	2.1 (1.7–2.5)	2.0 (1.6–2.4)	1.4 (1.2–1.6)
1.0 g/l	2.0 (1.7–2.4)	1.8 (1.5–2.0)	1.3 (1.0–1.5)
VE55, l/min			
0 g/l	33.2 (28.1–38.2)	33.4 (27.9–39.0)	18.6 (15.6–21.6)‡
0.5 g/l	33.9 (28.4–39.4)	33.5 (28.3–38.7)	16.3 (13.3–19.3)†
1.0 g/l	34.6 (29.5–39.8)	33.4 (29.4–37.4)	15.7 (12.7–18.6)†
Sedation score, mm			
0 g/l	8 (4–12)	12 (7–17)	47 (38–56)‡
0.5 g/l	5 (3–7)	12 (8–17)	45 (36–54)
1.0 g/l	4 (3–6)	16 (12–21)	46 (36–55)

Values are mean (95% CI), except for number of apneas, which are median (range); VE55 is the extrapolated ventilation at an end-tidal partial pressure of carbon dioxide of 55 mmHg and is derived from the estimated slope of the hypercapnic ventilatory response slope.

*$P < 0.01$ *vs.* control (0 g/l ethanol infusion without oxycodone). †$P < 0.01$ *vs.* oxycodone and 0 g/l concomitant ethanol infusion. ‡$P < 0.001$ *vs.* control.

HCVR = the hypercapnic ventilatory response; Pco_2 pressure of carbon dioxide.

Hypercapnic Ventilatory Response

Ethanol had no effect on the slope of the HCVR curve (table 2). Oxycodone did reduce the slope by 30 to 40% with no further effect from concomitant ethanol administration. The VE55 or the ventilation at an extrapolated end-tidal carbon dioxide concentration of 55 mmHg takes both the HCVR slope and its position into account, and hence gives a better reflection of the respiratory effect of the intervention. Oxycodone but not ethanol affected VE55 significantly with a 44% reduction relative to baseline values 60

Table 3. Number of Apneic Events in the Young Participants and Participants in the Elderly Group at the Three Breath Alcohol Concentrations Observed in Visits 1–3

	Baseline			Ethanol Infusion			Oxycodone Plus Ethanol Infusion		
Target breath alcohol concentration, g/l	0	0.5	1.0	0	0.5	1.0	0	0.5	1.0
Young participants (21–28 yr)									
Participant 1	0	1	2	1	4	1	0	1	0
Participant 2	0	0	0	0	0	1	0	0	0
Participant 3	0	0	2	0	0	0	0	0	0
Participant 4	1	4	1	0	0	0	0	0	0
Participant 5	0	1	0	1	0	0	0	0	0
Participant 6	0	0	0	0	0	1	0	0	0
Participant 7	0	0	2	0	1	1	0	2	1
Participant 8	0	0	0	0	1	8	0	1	7
Participant 9	0	0	1	0	5	3	0	0	1
Participant 10	0	0	1	0	0	1	0	0	0
Participant 11	0	0	0	0	1	0	0	0	0
Participant 12	0	0	0	0	0	0	0	0	1
Range	0–1	0–4	0–2	0–1	0–4	0–8	0–0	0–2	0–7
No. of subjects with > 2 apneic events	0	1	0	0	2	2	0	0	1
Participants in the elderly group (66–77 yr)									
Participant 13	0	0	0	0	0	0	0	0	0
Participant 14	0	0	1	0	1	1	1	1	5
Participant 15	0	0	3	0	0	3	0	0	2
Participant 16	0	0	1	0	0	0	0	0	1
Participant 17	1	0	2	0	1	3	0	0	11
Participant 18	1	0	1	0	1	6	0	2	3
Participant 19	0	0	0	0	0	1	0	0	0
Participant 20	0	0	1	0	0	1	0	0	5
Participant 21	0	0	2	0	0	3	0	0	2
Participant 22	0	0	3	0	0	1	0	3	4
Participant 23	0	0	1	1	1	8	0	0	11
Participant 24	0	0	1	1	0	8	0	0	11
Range	0–1	0–0	0–3	0–1	0–1	0–8	0–1	0–3	0–11
No. of subjects with > 2 apneic events	0	0	2	0	0	6	0	1	7

to 120 min after oxycodone intake ($P < 0.001$ *vs.* control). Adding ethanol further reduced VE55 to 52% (0.5 g/l) and 55% (1.0 g/l) of baseline values ($P < 0.01$ *vs.* control; fig. 4).

Variability

The variability data are given in fig. 5, A and B, which show that for tidal volume the mean %CV increased significantly to 55% (47 to 63%) at the combination of oxycodone and 1 g/l ethanol ($P < 0.01$ *vs.* oxycodone and oxycodone plus ethanol 0.5 g/l). Similar observations were made for breath time (the sum of inspiratory time and expiratory time) with the highest variability observed during the combination of oxycodone and 1 g/l ethanol (49% [41 to 57%], $P < 0.05$ *vs.* oxycodone).

Age Effect

Apart from number of apneic events and ventilation, no age effects were observed for any of the respiratory variables.

Discussion

We performed a proof-of concept trial on the coadministration of immediate release 20 mg oxycodone and two levels of ethanol (breath concentrations of 0.5 and 1.0 g/l) on the control of breathing in a mixed population of young and elderly opioid-naive participants. We observed that 20 mg oxycodone significantly reduced minute ventilation, the slope of the HCVR, and VE55. Baseline ventilation and VE55 were further impaired by the concomitant administration of ethanol, independent of dose. Especially, but not exclusively, in the elderly population, the ethanol oxycodone combination produced repeated apneic events (table 3) resulting in frequent episodes of oxygen desaturation.

Except for some small drops in Spo_2, we did not observe major effects of 0.5 and 1.0 g/l ethanol on ventilatory control. In contrast, when combined with oxycodone, ethanol enhanced the OIRD. Although our study was not mechanistic in nature, it is important to discuss possible underlying mechanisms. The lack of major effects on ventilatory control from ethanol (despite the occurrence of mild sedation) is in close agreement with previous observations, showing either no effect of ethanol on the control of breathing or some small stimulatory effects.[14–18] This may be related to a persistent rise in brain network activity, observed at low

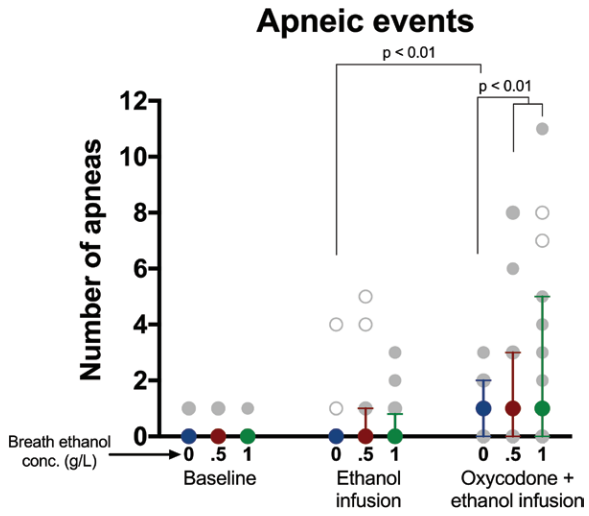

Fig. 3. Effect of 0, 0.5, 1 g/l ethanol (breath concentration), 20 mg oxycodone immediate release tablet, and their combination on apneic events. *Open circles* are the data from the young subject population, *closed gray circles* from the elderly population. *Blue* data points are median values ± interquartile range (IQR) at a breath ethanol concentration of 0 g/l; *red* data points are median values ± IQR at a breath ethanol concentration of 0.5 g/l; *green* data points are median values ± IQR at a breath ethanol concentration of 1 g/l.

ethanol concentrations.[30] The interactive effect on OIRD is likely due to an effect of ethanol on oxycodone pharmacokinetics or pharmacodynamics: (1) possibly ethanol increased the oxycodone concentration in plasma as is observed for other opioids although this is reported mostly after oral ethanol ingestion[31]; (2) ethanol may have increased the level of sedation induced by the opioid.[7] Although this did not seem the case in our study, as the level of self-reported sedation was not further increased by ethanol (table 2), the reliability of self-assessment may be diminished at higher ethanol levels with a false overoptimistic perception of functional ability commonly observed in young and older ethanol users.[8,32] Animal studies do indicate the enhancement of sedation as cause of ethanol–opioid interaction on OIRD[7]; (3) ethanol may have interacted with oxycodone at the level of the μ-opioid receptor.[33] Possible scenarios are the rapid sensitization of μ-opioid receptors by ethanol and/or ethanol-induced increase in density of opioid receptors in areas of the brain involved in the control of breathing; (4) finally, the negative effect of ethanol and oxycodone on ventilatory control may be due to the combination of ethanol-induced enhanced γ-aminobutyric acid–mediated and inhibited glutamatergic neurotransmission and opioid-induced opioidergic neuronal inhibition within the respiratory networks of the brainstem.[1,2,9,10] All of these mechanisms remain speculative at present, and further studies are required to understand the complex interaction of opioids and ethanol on the control of breathing in young and elderly humans. We relate the observation that the elderly population shows greater respiratory depression than our younger participants to the higher sensitivity of the elderly to opioids and ethanol, to their lesser resilience and physiologic reserve, and possibly to greater oxycodone plasma concentrations.[8,21,22]

We studied a single dose of oxycodone in opioid-naive individuals and therefore cannot predict the effect of ethanol on OIRD in chronic opioid users and abusers from our data. However, recent animal work indicates that tolerance to opioid analgesia is not associated with tolerance to the respiratory effects of opioids.[34] Moreover, ethanol interacts with synaptic transmission in opioid pathways and inhibits or reverses the development of tolerance to OIRD due to sensitization of μ-opioid receptors expressed on neurons in the respiratory centers of the brainstem.[33] Additionally, forensic studies show that ethanol is associated in a high percentage of opioid mortality cases.[5,6] We may assume that many of these fatalities were not naive to opioid consumption.[35] All together, these findings suggest that our experimental clinical study may be applicable to individuals who regularly consume opioids for medical or hedonistic reasons.

In common with previous observations in rodents and humans,[36,37] we observed an increase in respiratory

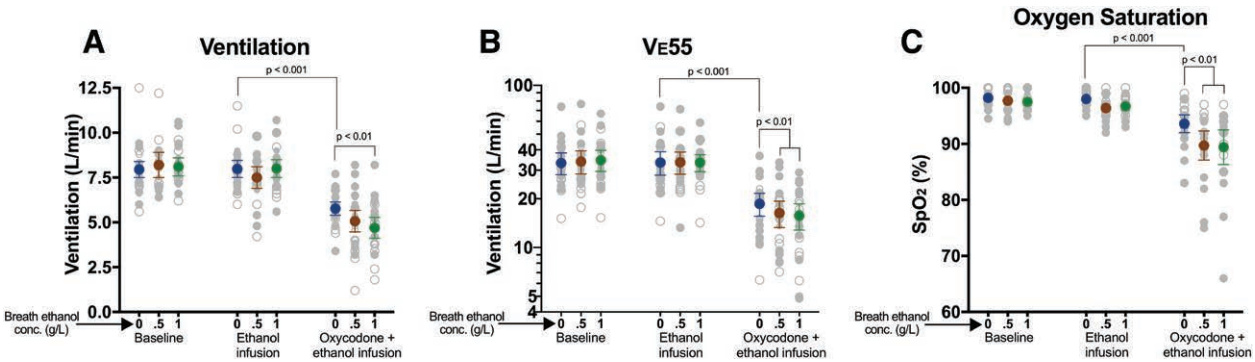

Fig. 4. Effect of 0, 0.5, 1 g/l ethanol (measured breath concentration), 20 mg oxycodone immediate release tablet, and their combination on minute ventilation (*A*), VE55 (*B*), and oxygen saturation (*C*). *Open circles* are the data from the young subject population, *closed gray circles* from the elderly population. *Blue* data points are mean values ± SD at a breath ethanol concentration of 0 g/l; *red* data points are mean values ± SD at a breath ethanol concentration of 0.5 g/l; *green* data points are mean values ± SD at a breath ethanol concentration of 1 g/l. Spo_2 = oxygen saturation measured by pulse oximetry.

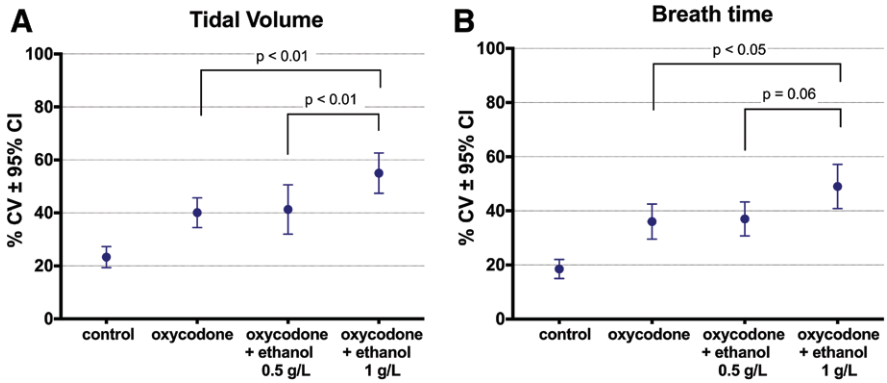

Fig. 5. Variability of tidal volume (*A*) and breath time (= inspiratory + expiratory time; *B*) during exposure to 20 mg oxycodone immediate release and the combination of 20 mg oxycodone and 0.5 and 1.0 g/l ethanol. Values are mean ± 95% CI. CV = coefficient of variation.

variability with oxycodone (fig. 5). Ethanol further increased the variability in tidal volume and breath time (the sum of inspiratory and expiratory times) with the greatest variability observed at the combination of oxycodone and 1 g/l ethanol. Importantly, the increase in respiratory variability preceded apneas in all volunteers independent of age. This indicates that variability may be an important predictor of the severity of OIRD and possibly also of imminent respiratory adverse events.

Study Limitations

The design of our study was dose escalating and single blind as requested by our IRB. The committee was most concerned with the safety of the elderly participants. We observed frequent apneic episodes in nine (*i.e.*, more than two events) elderly volunteers and episodes of low Spo_2 below 85% in two of these subjects. Due to our rapid intervention with supplemental oxygen and verbal stimulation, the drops in Spo_2 were short-lived. Therefore, it was decided, after consultation with the data safety monitoring board, to keep the subjects in the study and/or have them proceed to the next cohort. This chain of decision-making was the reason for nonrandomization. How much the absence of randomization and double blinding affected the outcome of our study remains unknown. We may assume that our safety interventions caused underestimation of the true respiratory depressant effects of oxycodone and ethanol treatment, especially in the elderly population.

We did not measure oxycodone concentrations in plasma. The pharmacokinetics of oral oxycodone is highly variable.[29] To take into account some of this variability, we measured the respiratory effects at multiple time points after oxycodone ingestion and report peak effect, which we associate with the peak concentration of the opioid at its target site. Further pharmacokinetic–pharmacodynamic modeling studies will enable the full characterization of the interactive effects of ethanol and oxycodone on the ventilatory control system. Our current study suggests an additive interaction of ethanol on OIRD; however, our data were obtained over a rather restrictive concentration range for obvious safety reasons. At higher ethanol and opioid concentrations, greater respiratory effects will occur due to a further increase in central nervous system depression (from both ethanol and opioids), loss of upper airway patency and further depression of respiratory centers in the brainstem. Given the safety issues observed, we do not believe that studies outside the concentration ranges tested by us in the current study, in especially elderly volunteers, are desirable.

In conclusion, our studies in healthy volunteers provide evidence that combining prescription opioids with ethanol leads to significant and clinically relevant levels of respiratory depression and increases the risk of toxicity through a pharmacologic interaction, an effect that is more pronounced in elderly individuals.

Research Support

Support was provided solely from institutional and/or departmental sources.

Competing Interests

Dr. Dahan is chairman of the Institutional Review Board of Leiden University but was not involved in the review of this study. The other authors declare no competing interests.

Reproducible Science

Full protocol available from Dr. Dahan: a.dahan@lumc.nl. Raw data available from Dr. Dahan: a.dahan@lumc.nl.

Correspondence

Address correspondence to Dr. Dahan: Department of Anesthesiology, Leiden University Medical Center, PO Box 9600, 2300 RC Leiden, The Netherlands. a.dahan@lumc.nl. This article may be accessed for personal use at no charge through the Journal Web site, www.anesthesiology.org.

References

1. Dahan A, Aarts L, Smith TW: Incidence, reversal, and prevention of opioid-induced respiratory depression. Anesthesiology 2010; 112:226–38
2. Pattinson KT: Opioids and the control of respiration. Br J Anaesth 2008; 100:747–58
3. Jones CM, Paulozzi LJ, Mack KA; Centers for Disease Control and Prevention (CDC): Alcohol involvement in opioid pain reliever and benzodiazepine drug abuse-related emergency department visits and drug-related deaths—United States, 2010. MMWR Morb Mortal Wkly Rep 2014; 63:881–5
4. Rockville M: The DAWN Report: Highlights of the 2011 Drug Abuse Warning Network (DAWN) Findings on Drug-Related Emergency Department Visits. Substance Abuse and Mental Health Services Administration, Center for Behavioral Health Statistics and Quality 2013. Available at: http://www.samhsa.gov/data/sites/default/files/DAWN127/DAWN127/sr127-DAWN-highlights.pdf. 2013. Accessed January 1, 2017.
5. Hickman M, Lingford-Hughes A, Bailey C, Macleod J, Nutt D, Henderson G: Does alcohol increase the risk of overdose death: The need for a translational approach. Addiction 2008; 103:1060–2
6. Levine B, Green D, Smialek JE: The role of ethanol in heroin deaths. J Forensic Sci 1995; 40:808–10
7. Corrigan F, Wu Y, Tuke J, Coller JK, Rice KC, Diener KR, Hayball JD, Watkins LR, Somogyi AA, Hutchinson MR: Alcohol-induced sedation and synergistic interactions between alcohol and morphine: A key mechanistic role for Toll-like receptors and MyD88-dependent signaling. Brain Behav Immun 2015; 45:245–52
8. Gilbertson R, Ceballos NA, Prather R, Nixon SJ: Effects of acute alcohol consumption in older and younger adults: Perceived impairment *versus* psychomotor performance. J Stud Alcohol Drugs 2009; 70:242–52
9. Franks NP, Lieb WR: Inhibitory synapses. Anaesthetics set their sites on ion channels. Nature 1997; 389:334–5
10. Mihic SJ, Ye Q, Wick MJ, Koltchine VV, Krasowski MD, Finn SE, Mascia MP, Valenzuela CF, Hanson KK, Greenblatt EP, Harris RA, Harrison NL: Sites of alcohol and volatile anaesthetic action on GABA(A) and glycine receptors. Nature 1997; 389:385–9
11. Marchenko V, Koizumi H, Mosher B, Koshiya N, Tariq M, Bezdudnaya T, Zhang R, Molkov Y, Rybak I, Smith J: Perturbations of respiratory rhythm and pattern by disrupting synaptic inhibition within pre-Bötzinger and Bötzinger complexes. eNeuro 2016; 3: 1–24
12. van der Schier R, Roozekrans M, van Velzen M, Dahan A, Niesters M: Opioid-induced respiratory depression: Reversal by non-opioid drugs. F1000Prime Rep 2014; 6:79
13. Setnik B, Sokolowska M, Johnson F, Oldenhof J, Romach M: Evaluation of the safety, pharmacodynamic, and pharmacokinetic effects following oral coadministration of immediate-release morphine with ethanol in healthy male participants. Hum Psychopharmacol 2014; 29:251–65
14. Higgins HL: Effect of alcohol on the respiration and the gaseous metabolism in man. J Pharmcol Exp Ther 1917; 9: 441–72
15. Bellville JW, Swanson GD, Miyake T, Aqleh KA: Respiratory stimulation observed following ethanol ingestion. West J Med 1976; 124:423–5
16. Bellville JW, Thompson JH: Effect of ethanol on peripheral and central chemoreflex loop gain in man. Proc West Pharmacol Soc 1980; 23:325–30
17. Zilm DH: Ethanol-induced spontaneous and evoked EEG, heart rate, and respiration rate changes in man. Clin Toxicol 1981; 18:549–63
18. van de Borne P, Mark AL, Montano N, Mion D, Somers VK: Effects of alcohol on sympathetic activity, hemodynamics, and chemoreflex sensitivity. Hypertension 1997; 29: 1278–83
19. Michiels TM, Light RW, Mahutte CK: Naloxone reverses ethanol-induced depression of hypercapnic drive. Am Rev Respir Dis 1983; 128:823–6
20. McCauley VB, Grunstein RR, Sullivan CE: Ethanol-induced depression of hypoxic drive and reversal by naloxone–A sex difference. Am Rev Respir Dis 1988; 137:1406–10
21. Aubrun F, Salvi N, Coriat P, Riou B: Sex- and age-related differences in morphine requirements for postoperative pain relief. Anesthesiology 2005; 103:156–60
22. Dufour MC, Archer L, Gordis E: Alcohol and the elderly. Clin Geriatr Med 1992; 8:127–41
23. Deyo RA, Hallvik SE, Hildebran C, Marino M, Dexter E, Irvine JM, O'Kane N, Van Otterloo J, Wright DA, Leichtling G, Millet LM: Association between initial opioid prescribing patterns and subsequent long-term use among opioid-naïve patients: A statewide retrospective cohort study. J Gen Int Med 2017; 32:21–7
24. Fulton-Kehoe D, Sullivan MD, Turner JA, Garg RK, Bauer AM, Wickizer TM, Franklin GM: Opioid poisonings in Washington State Medicaid: Trends, dosing, and guidelines. Med Care 2015; 53:679–85
25. Chung F, Abdullah HR, Liao P: STOP-Bang Questionnaire: A practical approach to screen for obstructive sleep apnea. Chest 2016; 149:631–8
26. Zoethout RW, van Gerven JM, Dumont GJ, Paltansing S, van Burgel ND, van der Linden M, Dahan A, Cohen AF, Schoemaker RC: A comparative study of two methods for attaining constant alcohol levels. Br J Clin Pharmacol 2008; 66:674–81
27. Dahan A, Nieuwenhuijs D, Teppema L: Plasticity of central chemoreceptors: Effect of bilateral carotid body resection on central CO2 sensitivity. PLoS Med 2007; 4:e239
28. Zuurman L, Roy C, Schoemaker RC, Hazekamp A, den Hartigh J, Bender JC, Verpoorte R, Pinquier JL, Cohen AF, van Gerven JM: Effect of intrapulmonary tetrahydrocannabinol administration in humans. J Psychopharmacol 2008; 22:707–16
29. Olesen AE, Upton R, Foster DJ, Staahl C, Christrup LL, Arendt-Nielsen L, Drewes AM: A pharmacokinetic and pharmacodynamic study of oral oxycodone in a human experimental pain model of hyperalgesia. Clin Pharmacokinet 2010; 49:817–27
30. Korkotian E, Bombela T, Odegova T, Zubov P, Segal M: Ethanol affects network activity in cultured rat hippocampus: Mediation by potassium channels. PLoS One 2013; 15: 1–11
31. Lennernäs H: Ethanol-drug absorption interaction: Potential for a significant effect on the plasma pharmacokinetics of ethanol vulnerable formulations. Mol Pharm 2009; 6:1429–40
32. Tiplady B, Franklin N, Scholey A: Effect of ethanol on judgments of performance. Br J Psychol 2004; 95(Pt 1):105–18
33. Hill R, Lyndon A, Withey S, Roberts J, Kershaw Y, MacLachlan J, Lingford-Hughes A, Kelly E, Bailey C, Hickman M, Henderson G: Ethanol reversal of tolerance to the respiratory depressant effects of morphine. Neuropsychopharmacology 2016; 41:762–73
34. Emery MJ, Groves CC, Kruse TN, Shi C, Terman GW: Ventilation and the response to hypercapnia after morphine in opioid-naive and opioid-tolerant rats. Anesthesiology 2016; 124:945–57
35. Saunders KW, Von Korff M, Campbell CI, Banta-Green CJ, Sullivan MD, Merrill JO, Weisner C: Concurrent use of alcohol and sedatives among persons prescribed chronic opioid therapy: Prevalence and risk factors. J Pain 2012; 13:266–75
36. Bouillon T, Bruhn J, Roepcke H, Hoeft A: Opioid-induced respiratory depression is associated with increased tidal volume variability. Eur J Anaesthesiol 2003; 20:127–33
37. Fechtner L, El Ali M, Sattar A, Moore M, Strohl KP: Fentanyl effects on breath generation in C57BL/6J and A/J mouse strains. Respir Physiol Neurobiol 2015; 215:20–9