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RESPIRATION AND THE AIRWAY

High-inspired oxygen concentration further impairs opioid-induced respiratory depression

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Editor's key points

- It is important to understand the effects of opioids on ventilatory parameters.
- This study investigated the ventilatory effects of opioids under different inspired oxygen concentrations.
- Increased inspired oxygen resulted in greater opioid-induced respiratory depression.
- Opioid-related respiratory depression was not detected by Sp_{O_2} monitoring when supplemental oxygen was given.

Background. Hyperoxaemia depresses the output of peripheral and central chemoreceptors. Patients treated with opioids often receive supplemental oxygen to avert possible decreases in oxygen saturation (Sp_{O_2}). We examined the effect of a single dose of remifentanil in healthy volunteers inhaling room air *vs* air enriched with 50% oxygen.

Methods. Twenty healthy volunteers received i.v. 50 μg remifentanil (infused over 60 s) at anormoxic (N) or hyperoxic ($F_{I_{O_2}}$ 0.5, H) background on separate occasions. Minute ventilation (Vi), respiratory rate (RR), end-tidal P_{CO_2}, and Sp_{O_2} were collected on a breath-to-breath basis. The occurrence of apnoea was recorded.

Results. During normoxia, remifentanil decreased Vi from 7.4 (1.3) [mean (SD)] to 2.2 (1.2) litre min^{-1} ($P<0.01$), and during hyperoxia from 7.9 (1.0) to 1.2 (1.2) litre min^{-1} ($P<0.01$; H *vs* N: $P<0.001$). RR decreased from 13.1 (2.9) to 6.1 (2.8) bpm during N ($P<0.01$) and from 13.2 (3.0) to 3.6 (4.0) bpm during H ($P<0.01$; H *vs* N: $P<0.01$). During normoxia, Sp_{O_2} decreased from 98.4 (1.5) to 88.6 (6.7)% ($P<0.01$), while during hyperoxia, Sp_{O_2} changed from 99.7 (0.7) to 98.7 (1.0)% ($P<0.001$). Apnoea developed in two subjects during normoxia and 10 during hyperoxia.

Conclusions. Respiratory depression from remifentanil is more pronounced in hyperoxia than normoxia as determined from minute ventilation, end-tidal P_{CO_2}, and RR. During hyperoxia, respiratory depression may be masked when measuring Sp_{O_2} as pulse oximetry remains in normal values during the first minutes of respiratory depression.

Keywords: analgesics; hyperoxia; hypoventilation; hypoxia; monitoring; opioids; oxygen; remifentanil; respiration; respiratory depression; respiratory rate; ventilatory depression

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Opioids are essential instruments in the treatment of moderate-to-severe pain. However, the use of opioids comes with a variety of side-effects; of which, opioid-induced respiratory depression is potentially life-threatening.[1] Spontaneously breathing patients on opioid therapy often receive supplemental oxygen to prevent the occurrence of decreases in Sp_{O_2}. Oxygen is a potent modifier of the ventilatory control system.[2 3] It directly interacts with breathing by decreasing the activity of the peripheral chemoreceptors at the carotid bodies and modifies central drive by decreasing the slope of the ventilatory carbon dioxide response of the central chemoreceptors in the brainstem.[2] Little is known on the interaction of high-inspired oxygen concentration and opioid therapy on breathing. Since opioids activate μ-opioid receptors expressed on neurones in brain areas involved in chemosensitivity and rythmogenesis,[4] it is reasonable to assume that they interact in their effects on breathing.

In the current proof-of-concept study, we measured the effect of a single bolus dose of remifentanil (50 μg) on ventilation in healthy volunteers inhaling a normoxic *vs* a hyperoxic gas mixture. We tested the opioid remifentanil, as this opioid is short acting, a potent depressant of ventilation, and is increasingly used in spontaneously breathing patients for a variety of indications, including labour pain, procedural analgesia and sedation, and postoperative pain relief.[5–8]

We hypothesize that remifentanil during hyperoxia impairs ventilation more than during normoxia, due to the combined effects of remifentanil and oxygen.

Methods

Testing the effect of the inspired oxygen condition on opioid-induced respiratory depression was the primary endpoint of the study. Furthermore, a secondary endpoint of the study was the ability of reductions in minute ventilation

to be detected by coincident reductions in respiratory rate (RR) and/or oxygen saturation as displayed on monitoring equipment.

Volunteers

Twenty healthy male (n=10) and female (n=10) volunteers (aged 18–28 yr, BMI 23–29 kg m^{-2}, weight 73–89 kg) were enrolled in the study after approval of the protocol by the Human Ethics Committee of the LUMC (CommissieMedischeEthiek, LUMC, Leiden, The Netherlands). All subjects gave informed consent before the measurements.

Study design

During breathing of either a normoxic gas mixture (inspired fraction 0.21) or a hyperoxic gas mixture (inspired fraction 0.5), the subjects received an i.v. infusion of 50 μg remifentanil (Ultiva, GlaxoSmithKline, Zeist, The Netherlands) over 90 s. From 5 min before the opioid administration until 10 min after the start of drug infusion, the following parameters were measured and collected on a breath-to-breath basis for further analysis: minute ventilation (Vi), tidal volume, inspired and end-tidal oxygen concentrations, end-tidal P_{CO_2}, RR (F), and Sp_{O_2}. All subjects breathed through a facemask connected to a pneumotachograph and differential pressure transducer (#4813, Hans Rudolph, Myandotta, MI, USA). The pneumotachograph was connected to a custom-made gas mixing system that was connected to oxygen, nitrogen, and carbon dioxide gas containers via three mass-flow controllers (Bronkhorst High-Tec, Veenendaal, The Netherlands). The mass-flow controllers were controlled by a computer allowing the inhalation of preset inhaled gas mixtures. The airway gas flow signal of the pneumotachograph was integrated to yield a volume signal. The signal was calibrated with a motor-driven piston pump (volume 1 litre at 20–30 strokes min^{-1}). Corrections in volume were made for changes in gas viscosity due to changes in inhaled oxygen concentration. Inspired and expired oxygen and carbon dioxide concentration were measured with a Capnomac monitor (Datex, Helsinki, Finland). Sp_{O_2} was measured with a finger pulse oximeter (Masimo, Irvine, CA, USA). Each subject performed two experiments, one during the inhalation of a normoxic gas mixture (normoxia) and the other during inhalation of a hyperoxic gas mixture (inspired fraction 0.5) with 10–20 min between experiments. The sequence between runs was randomized. Oxygen inhalation preceded the drug infusion by 15 min. Heart rate and ECG were monitored throughout the studies.

Apnoea

Apnoea is defined in our study as the absence of spontaneous breathing as detected by the absence of flow through the pneumotachograph for at least 20s. In case the apnoeic episode lasted for 90 s, the subject was encouraged to take one or multiple breaths.

Power and statistical analysis

The study was powered (based on data on remifentanil effect on breathing from our laboratory)[8] to detect a difference in minute ventilation of 2 litre min^{-1} between normoxia and hyperoxia with an SD of 3 litre min^{-1}, α=0.05, and β=0.8. This resulted in a sample size of 20 (Sigmplot v 12 for Windows, Systat Software, Inc., San Jose, CA, USA).

The data were averaged over 1 min periods. The following two intervals were used in the data analysis: baseline (obtained during the 1 min period before drug infusion) and peak ventilatory depression (the 1 min in which the measured variable displayed its lowest, for Vi, F, and Sp_{O_2}, or highest, for end-tidal P_{CO_2}, value). The effects of remifentanil and oxygen treatment on Vi, F, end-tidal P_{CO_2}, and Sp_{O_2} were tested by the two-tailed paired t-tests or Wilcoxon signed-rank tests, with $P<0.05$ considered significant. The analyses were performed in SigmaPlot version 12 for Windows (Systat Software, Inc.). Data are presented as mean (SD) unless otherwise stated.

Results

The mean (SD) pre-drug baseline variables not affected by oxygen therapy were inspired minute ventilation [normoxic Vi 7.4 (1.3) litre min^{-1} and hyperoxic Vi 7.9 (1.0) litre min^{-1}], RR [normoxic F 13.1 (2.9) bpm and hyperoxic F 13.2 (3.0) bpm], and end-tidal P_{CO_2} [normoxia 5.1 (0.5) kPa and hyperoxia 5.2 (0.4) kPa]. End-tidal P_{O_2} varied between oxygen conditions: 13.3 (0.5) and 40 (1.0) kPa in normoxia and hyperoxia, respectively. Similarly, Sp_{O_2} was greater during hyperoxia: normoxic Sp_{O_2} 98.4 (1.5) % and hyperoxic Sp_{O_2} 99.7 (0.7)% ($P<0.05$).

The effect of the oxygen condition on remifentanil-induced respiratory depression is shown in Figure 1 and Table 1. Two subjects developed apnoea during normoxia,

Table 1 Effect of remifentanil on respiratory variables. Values are mean (SD). *$P<0.01$ *vs* baseline. #$P<0.05$ *vs* normoxic baseline. Baseline=1 min average before drug infusion. Peak effect=1 min average of data with lowest value after drug infusion. N, normoxia; H, hyperoxia

	Normoxia		Hyperoxia		Peak effect
	Baseline	Peak effect	Baseline	Peak effect	H *vs* N
Ventilation (litre min^{-1})	7.4 (1.3)	2.2 (1.2)*	7.9 (1.0)	1.2 (1.2)*	$P<0.01$
Respiratory rate (bpm)	13.1 (2.9)	6.1 (2.8)*	13.2 (3.0)	3.6 (4.0)*	$P<0.01$
Sp_{O_2} (%)	98.4 (1.5)	88.6 (6.7)*	99.7 (0.7)#	98.7 (1.0)	$P<0.001$
End-tidal P_{CO_2} (kPa)	5.1 (0.5)	5.7 (0.3)*	5.2 (0.4)	6.1 (0.6)*	$P<0.01$