BJA

British Journal of Anaesthesia, ■ (■): 1–11 (2018)

doi: 10.1016/j.bja.2018.02.021
Advance Access Publication Date: xxx
Laboratory Investigation

LABORATORY INVESTIGATION

Esketamine counters opioid-induced respiratory depression

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Abstract

Background: Opioids can produce life-threatening respiratory depression. This study tested whether subanaesthetic doses of esketamine stimulate breathing in an established human model of opioid-induced respiratory depression.
Methods: In a study with a randomised, double blind, placebo controlled, crossover design, 12 healthy, young volunteers of either sex received a dose escalating infusion of esketamine (cumulative dose 40 mg infused in 1 h) on top of remifentanil-induced respiratory depression. A population pharmacokinetic-pharmacodynamic analysis was performed with sites of drug action at baseline ventilation, ventilatory CO_2-chemosensitivity, or both.
Results: Remifentanil reduced isohypercapnic ventilation (end-tidal PCO_2 6.5 kPa) by approximately 40% (from 20 to 12 litre min^{-1}) in esketamine and placebo arms of the study, through an effect on baseline ventilation and ventilatory CO_2 sensitivity. The reduction in ventilation was related to a remifentanil effect on ventilatory CO_2 sensitivity (~39%) and on baseline ventilation (~61%). Esketamine increased breathing through an exclusive stimulatory effect on ventilatory CO_2 sensitivity. The remifentanil concentration that reduced ventilatory CO_2 sensitivity by 50% (C_{50}) was doubled at an esketamine concentration of 127 (84-191) ng ml^{-1} [median (interquartile range)]; the esketamine effect was rapid and driven by plasma pharmacokinetics. Placebo had no systematic effect on opioid-induced respiratory depression.
Conclusions: Esketamine effectively countered remifentanil-induced respiratory depression, an effect that was attributed to an increase in remifentanil-reduced ventilatory CO_2 chemosensitivity.

Keywords: esketamine; opioid; respiratory compromise; respiratory depression; reversal

The observation that opioids produce life-threatening respiratory depression is not new. The first reported death from i.v. morphine dates from the 1850s when Englishman Alexander Wood injected his wife with morphine just after the introduction of the hollow needle.[1] Public awareness of the potentially life-threatening adverse effects of opioids is new, however, and is related to the recent escalation of prescribed opioid consumption and prescribed opioid deaths in the USA and other western countries.[2–4] The combination of opioid misuse and cardiorespiratory depression in particular is potentially lethal. While it is well established that the increase in deaths occurs in patients that consume opioids in the community (i.e. opioids prescribed for treatment of chronic pain), opioid-induced respiratory depression (OIRD) is an equally relevant problem for patients treated with potent opioids in the acute or hospital setting.[5–7]

In recent years, various pharmacological interventions have been proposed to offset OIRD, most of which are respiratory stimulants that do not interact with the opioid receptor system, so that opioid analgesia is not compromised.[8] While

Editorial decision: February 17, 2018; **Accepted:** February 17, 2018

Editor's key points

- The authors tested whether subanaesthetic doses of esketamine (S(+) enantiomer of ketamine) stimulate breathing during opioid-induced respiratory depression in healthy human volunteers.
- Pharmacokinetic–pharmacodynamic analyses were undertaken to establish whether esketamine affected baseline ventilation and/or ventilatory CO_2-chemosensitivity.
- Esketamine dose-dependently increased breathing only during opioid induced ventilatory depression, exclusively through a stimulatory effect on ventilatory CO_2 sensitivity.
- Low-dose ketamine may be an effective strategy to reduce ventilatory depression after opioid administration.

some of these drugs are registered respiratory stimulants (e.g. doxapram), others are experimental drugs that require further research (ampakines, 5HT-agonsists, methylxanthines, drugs acting at background potassium channels of type 1 carotid body cells).[8–11] In the current study, we assess whether the commonly used anaesthetic esketamine is able to reverse, at subanaesthetic dose, (part of) the respiratory depression induced by a potent opioid. Recent animal and human data suggest that ketamine is a respiratory stimulant and consequently may possibly offset OIRD.[12–15] Ketamine is different from other respiratory stimulants in that it has inherent analgesic properties. Consequently, if ketamine is able to reverse OIRD, it may also reduce opioid consumption.[16]

We performed two studies. The first was a double blind, randomised, placebo-controlled, crossover trial designed as a proof-of-concept study to investigate the effect of dose-escalating infusions of esketamine (four steps with a cumulative dose of 40 mg per 70 kg given in 1 h) on opioid-induced respiratory depression under isohypercapnic conditions. We measured esketamine plasma concentrations and minute ventilation and performed a population pharmacokinetic (PK)–pharmacodynamic (PD) analysis. We hypothesise that (low-dose) esketamine will effectively reduce remifentanil-induced respiratory depression. To further understand esketamine's effect on ventilation, we next examined, in an observational study, whether esketamine is a respiratory stimulant when respiration is not depressed by an opioid.

Methods

Ethics and subjects

This single-centre, double blind, placebo-controlled, crossover study protocol was performed from November 2016 to July 2017 at the Anesthesia and Pain Research Unit of the Department of Anesthesiology at the Leiden University Medical Center. The local Institution Review Board (Commissie Medische Ethiek, Leiden, The Netherlands) and the Central Committee on Research involving Human Subjects (CCMO, The Hague, The Netherlands) approved the study protocol. Written informed consent was obtained from all participants before enrolment. All study procedures were conducted according to good clinical practice guidelines and adhered to the tenets of the Declaration of Helsinki. Participants were recruited by flyers posted on the campus of the university. The study was registered in the Dutch trial register (identifier 6248).

Healthy volunteers, aged 18–40 yr, with a body mass index <30 kg m^{-2} and able to read and understand the subject information form were recruited. Exclusion criteria were: a medical history of medical or psychiatric disease; any allergy to food or medication; alcohol abuse (i.e. >21 units per week); smoking; pregnancy or lactation; participation in an investigational drug trial in the 3 months before the current study; illicit drug use in the 30 days before the current study; or a positive urine dipstick on the screening or study days. The dipstick (Alere Toxicology Plc, Oxfordshire, UK) tests for cocaine, amphetamine, cannabinoids, phencyclidine, methadone, benzodiazepine, tricyclic antidepressants, and barbiturates. Subjects were asked not to eat and drink for 8 h before dosing, not to take caffeinated drinks, chocolate drinks or alcohol for 24 h before dosing and to refrain from grapefruit (juice) for 7 days before the first study visit and thereafter for the duration of the study.

Study design

Subjects visited the research unit on three separate occasions, at least 1 week apart. On visits 1 and 2, the effect of esketamine (Ketanest-S, Pfizer, The Netherlands) on opioid-induced respiratory depression was tested using a double-blind placebo-controlled, crossover design. Subjects were randomised to receive either esketamine or placebo (normal saline) on top of remifentanil (GlaxoSmithKline BV, The Netherlands) induced respiratory depression. On the third occasion, the effect of just esketamine on ventilation was studied (i.e. without remifentanil). Subjects received two i.v. access lines (one for esketamine or placebo and the other for remifentanil infusion) and a 22 G cannula in the left or right radial artery for blood sampling. During the study day, subjects were monitored by ECG, oxygen saturation via a finger probe and blood pressure through the arterial line.

Drug administration

Remifentanil was administered i.v. by target-controlled infusion on visits 1 and 2 (Supplementary Fig. S1). The remifentanil target controlled infusion system makes use of Minto and colleagues'[17] pharmacokinetic data set. The target concentration was started at 0.5 ng ml^{-1} and step-wise increased to a specific end-point (i.e. a decrease in ventilation by 40–50% of baseline value). Titration to effect was performed with steps in target remifentanil concentration of 0.1–0.5 ng ml^{-1}. After ventilation had reached a steady state for at least 10 min, the esketamine/placebo infusion began. Esketamine or placebo were administered by i.v. dose-escalating infusions over 60 min: 0–15 min 4 mg (step 1), 15–30 min 8 mg (step 2), 30–45 min 12 mg (step 3) and 45–60 min 16 mg (step 4); all doses are per 70 kg. After the 1 h esketamine infusion, the remifentanil infusion continued for another 15 min (see also Fig. 1). In case ventilation reached baseline values during steps 1, 2, or 3, a next step increase in ketamine was not performed and the esketamine infusion was ended at the end of the 15 min infusion of that particular step.

Ventilation measurements

On all three occasions, ventilation was measured on a breath-to-breath basis using the Dynamic End-Tidal Forcing