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Respiration and Airway

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

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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

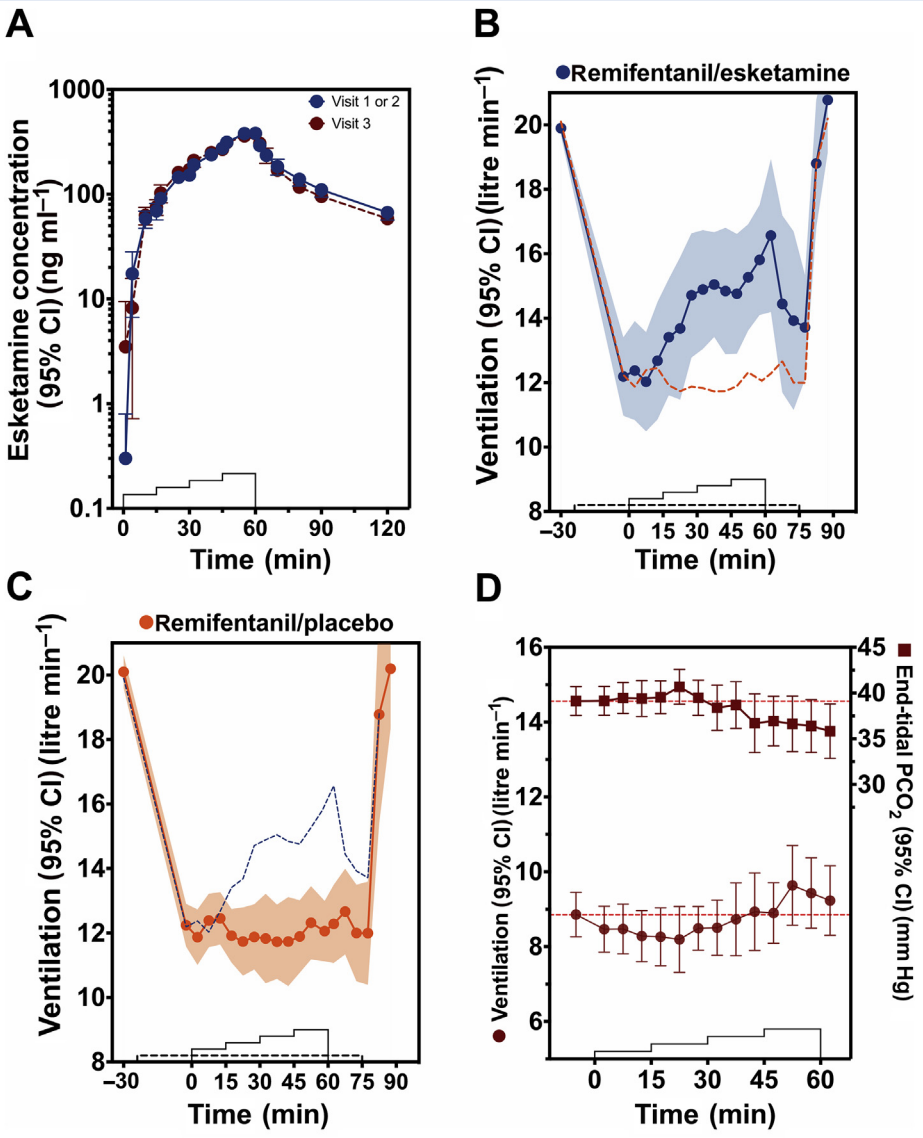

Fig 1. (A) Population averages of the plasma esketamine concentration of visits 1 or 2 (blue symbols) and visit 3 (red symbols). (B) The effect of esketamine on remifentanil-induced respiratory depression. To guide the eye, the placebo data are plotted on top of the esketamine data (orange broken line). (C) The effect of placebo on remifentanil-induced respiratory depression. To guide the eye, the remifentanil data are plotted on top of the placebo data (blue broken line). (D) The results of the observational trial of visit 3. All data are mean with 95% confidence interval (CI). The black lines are the esketamine infusion scheme, the broken black lines the remifentanil infusions. The dotted red lines in (D) reflect the baseline values of ventilation and end-tidal PCO_2.

technique.[18] Subjects breathed through a facemask connected to a pneumotachograph (#4813; Hans Rudolph Inc., Shawnee, KS, USA). The inhaled gas mixture came from three mass flow controllers (for O_2, N_2, and CO_2; Bronkhorst High-Tech BV, The Netherlands) that were controlled using custom-made software (RESREG/ACQ, Leiden University, Leiden, Netherlands). On visits 1 and 2 the inspired CO_2 concentration was manipulated to elevate and clamp the end-tidal PCO_2 to a level that caused an increase in mean [standard deviation (SD)] ventilation to 20 (2) litre min^{-1}, while end-tidal PO_2 was strictly maintained at a normoxic value (14.5 kPa). When ventilation reached a steady state under these isohypercapnic and iso-oxic conditions the remifentanil infusion was started followed by the esketamine or placebo infusion. After the remifentanil infusion had ended, ventilation measurements at isohypercapnic and iso-oxic conditions continued for another 15 min.

On the third visit, ventilation was measured under poikilocapnic conditions (i.e. without CO_2 clamping). The esketamine administration was similar to the infusion scheme of visit 1 or 2, however, without administration of remifentanil. Minute ventilation and end-tidal PCO_2 averages were calculated and used in the data analysis.

Sedation and drug high assessment

At the end of drug infusion, sedation and drug high were measured on an 11-point verbal rating scale (VRS) ranging from 0 (no effect) to 10 (maximum effect).

Blood sampling

To quantify the esketamine concentrations, arterial blood samples were collected in 6-ml heparin tubes. Blood samples were obtained at baseline (before any esketamine infusion) and t=1, 4, 10, 15, 17, 25, 30, 32, 40, 45, 47, 55, 60, 62, 65, 70, 80, 90, and 120 min after the start of esketamine infusion (Supplementary Fig. S1). Within 30 min after collection, blood samples were centrifuged at 450 g for 15 min at 4°C; 2–3 ml plasma was separated and stored at −80°C until analysis. Esketamine measurements were performed at the University of Groningen on a TSQ Quantum™ Access MAX Triple Quadrupole mass spectrometer (Thermo Fisher Scientific, Waltham, MA, USA) using a Vanquish autosampler (Thermo Fisher Scientific) and injections of 5 µl. The linear range of the assay was 2.5–2000 ng ml^{-1}; the lower limit of quantitation was 0.5 ng ml^{-1} for esketamine. The data were analysed using Xcalibur software (Thermo Fisher Scientific).

Randomisation and allocation

Randomisation was performed using a computer-generated randomisation list by an individual not involved in the study after all relevant parties (institutional and national review boards, pharmacy, departmental research board) approved the study protocol. The randomisation list was used by the pharmacy to prepare the study medication. The researchers notified the pharmacy of the subject number on the day before the study. Esketamine or saline were delivered to the laboratory on the morning of the study in syringes labelled with subject and visit numbers (1 or 2) only. The research team prepared all other medication. The team remained blinded to treatment until the data acquisition was completed.

Data analysis

A population PK–PD model was constructed in which the esketamine's PK was linked to the remifentanil potency parameter (i.e. C_{50} or the concentration remifentanil that reduced ventilation by 50%). The population analyses were performed in NONMEM version 7.4.1 (software for nonlinear mixed effects modelling; Icon plc, Gaithersburg, MD, USA). Model selection was based on the minimum objective function value (χ^2 test), standard error of estimates (SEE) and goodness of fit plots. For both PK and PD analysis, the model parameters were assumed to be log-normally distributed across the population. Residual error was assumed to have both an additive and a relative error for concentrations and only an additive error for ventilation. All values in the PK–PD analysis are median (SEE = standard error of the estimate); *P*-values < 0.01 were considered significant.

The analyses were performed simultaneously on remifentanil/esketamine and remifentanil/placebo data in multiple steps (with estimation of interoccasion variability for the remifentanil model parameters). (i) First the esketamine PK data were analysed using a three-compartment model. Initially, the structural parameters of Sigtermans and colleagues[19] were implemented, after which we searched for systematic deviations from that model. (ii) For remifentanil, it was assumed that the target-controlled infusion values correctly reflect the plasma concentrations. (iii) For both esketamine (E) and remifentanil (R), a possible hysteresis between plasma concentration and effect was modelled by assuming effect compartments with blood-effect-site equilibration half-times, $t_{½E}$ and $t_{½R}$, respectively. (iv) Next, the population PD model parameters were determined with fixed empirical Bayesian individual drug PK model parameters.

Inspired minute ventilation ($\dot{V}_E$) was modelled as[20]:

$$\dot{V}_E = \dot{V}_{BLN} + S \times (P_TCO_2 - P_{TB}CO_2) \quad (1)$$

where $\dot{V}_{BLN}$ is baseline ventilation obtained without any inspired CO_2, S the ventilatory carbon dioxide sensitivity, P_TCO_2 the CO_2 concentration at the site of chemoreception (and instantaneously related to $\dot{V}_E$) and $P_{TB}CO_2$ the baseline value of P_TCO_2. In our isohypercapnic experiments, P_TCO_2 was assumed to be constant over time, hence (P_TCO_2–$P_{TB}CO_2$) is a constant. We next assume that remifentanil depresses ventilation by an effect on $\dot{V}_{BLN}$, S, or both:

$$Y1 = \dot{V}_{BLN} \Big/ \left[1 + (C_{REM}/C_{50}1)^{G1}\right] \quad (2)$$

$$Y2 = S \Big/ \left[1 + (C_{REM}/C_{50}2)^{G2}\right] \quad (3)$$

and

$$\dot{V}_E = (1 - \lambda) \times Y1 + \lambda \times Y2 \quad (4)$$

where C_{REM} is the remifentanil effect-site concentration and $C_{50}1$ the concentration remifentanil that $\dot{V}_{BLN}$ by 50%, $C_{50}2$ the concentration remifentanil that reduces S by 50%, G1 and G2 shape factors and λ a constant. Since the effect of remifentanil on S and $\dot{V}_{BLN}$ may effectively occur at separate sites in the brainstem, we postulated two distinct equilibration half-times, $t_{½R1}$ and $t_{½R2}$.

We assume that esketamine may increase $C_{50}1$ or $C_{50}2$ as follows:

$$C_{50}1 = C_{50}1(0) \times \left[1 + \left(C_{KET}/C_D^K1\right)^Q\right] \quad (5)$$

$$C_{50}2 = C_{50}2(0) \times \left[1 + \left(C_{KET}/C_D^K2\right)^Q\right] \quad (6)$$

where $C_{50}1(0)$ and $C_{50}2(0)$ are the respective remifentanil $C_{50}1$ and $C_{50}2$ values when the esketamine effect-site concentration is zero, C_{KET} the esketamine effect-site concentration, C_D^K1 and C_D^K2 the esketamine effect-site concentrations causing a doubling of $C_{50}1$ and $C_{50}2$, respectively, and Q a shape factor.

The effect of placebo on remifentanil-induced respiratory depression was modelled as follows:

$$C_{50}2 = C_{50}2(0) \times \left[1 + \left(C_P/C_D^K2\right)^Q\right] \quad (7)$$

where C_P is the assumed esketamine concentration during placebo treatment.

A mixture analysis was performed on C_D^K2 with four possible response subgroups. An individual can be a ketamine responder or non-responder, and a placebo responder or non-responder, giving four possibilities. The mixture analysis was done in NONMEM, by specifying: (i) the probability of being a ketamine responder and the probability of being a placebo responder; and (ii) the C_D^K2 values of the four subgroups: an

estimable parameter for ketamine, an estimable parameter for placebo, and a fixed potency of zero (corresponding to a C_D^K2 of infinity) for the (ketamine and placebo) non-responders. The probability parameters are estimated by NONMEM by minimising the objective function as usual. In addition, NONMEM estimates to which of the four subgroups the individuals are the most likely to belong, on the basis of which the ketamine/placebo responder/non-responder status of the subjects were assessed and counted. The choice of C_D^K2 for mixture analysis was based on the objective functions of the various models that were tested. These models included: (i) a model in which remifentanil had an effect at a single component Y *vs* an effect at Y1 and Y2; (ii) a model with an esketamine effect on C_D^K1 and C_D^K2 with $C_D^K1 = C_D^K2$ *vs* an effect at just C_D^K2; (iii) a model with an esketamine effect on C_D^K1 and C_D^K2 with $C_D^K1 \neq C_D^K2$ *vs* an effect at just C_D^K2; (iv) a model in which Q was not fixed *vs* Q fixed to 1; (v) a model in which esketamine was compared with placebo without any mixture analysis *vs* the mixture analysis as described above; and (vi) a model in which placebo and esketamine data were grouped with a mixture analysis with two possible groups (responders and non-responders) *vs* a model with mixture analysis with four groups as described above.

We calculated normalised prediction discrepancies (NPD; by NONMEM) as a visual predictive check of the final esketamine model.[21,22] In brief, 300 Monte Carlo simulations (of the final model output based on the fixed and distributions of the random effects) were performed and the number of times an observation is greater than the model prediction is counted. The NPD are the counts divided by 300, transformed via the inverse normal distribution. Under the null hypothesis that the model is correct, the NPD should have a normal distribution. It was checked by visual inspection that the NPD *vs* time showed no trends, heteroscedasticity, or both.

Results

Sixteen subjects of either sex were enrolled in the study. Two subjects ended their participation during screening because of facemask discomfort, two others because of esketamine-induced psychomimetic side effects. Their data were discarded. The 12 participating subjects (six men, six women) had a mean age of 24 (range 20–31) yr, weight of 68 (52–102) kg and body mass index of 22 (19–30) kg m^{-2}. All 12 subjects completed the study without major side effects.

Side effects

Side effects included nausea (occurred on seven occasions), headache (two occasions) and anxiety (one occasion). Mean drug high VRS scores (SD) were: remifentanil/esketamine 7.2 (1.9), remifentanil/placebo 1.9 (2.3; $P<0.001$ *vs* remifentanil/esketamine) and esketamine (visit 3) 6.9 (2.5; $P=0.75$ *vs* remifentanil/esketamine). Sedation VRS scores were remifentanil/esketamine 7.0 (2.5), remifentanil/placebo 3.7 (2.4; $P<0.001$ *vs* remifentanil/esketamine) and esketamine (visit 3) 6.3 (2.6; $P=0.18$ *vs* remifentanil/esketamine).

Effect of esketamine *vs* placebo on remifentanil-induced respiratory depression

The average esketamine concentrations are given in Figure 1A; mean (SD) peak plasma esketamine concentration was 381 (65) ng ml^{-1}. The end-tidal PCO_2 values were similar between treatments: mean end-tidal PCO_2 esketamine 6.6 (0.4) kPa *vs* placebo 6.5 (0.5) kPa ($P=0.20$). The target remifentanil concentration was somewhat higher in the esketamine arm [1.0 (0.4) ng ml^{-1}] compared with the placebo arm [0.90 (0.3) ng ml^{-1}, $P=0.01$].

Figure 1B and C demonstrate that esketamine but not placebo antagonised remifentanil-induced respiratory depression. Remifentanil had similar effects in the two arms of the study with a reduction from 19.9 (0.4) to 12.2 (2.3) litre min^{-1} in the esketamine arm and from 20.1 (0.9) to 12.2 (1.3) litre min^{-1} in the placebo arm of the study. Adding placebo had no effect on remifentanil-induced respiratory depression [change in ventilation from 12.2 (1.3) to 12.3 (2.2) litre min^{-1}]. In contrast, esketamine increased ventilation from 12.2 (2.3) to 16.6 (4.1) litre min^{-1} (an increase of 35%; paired *t*-test: $P<0.01$ *vs* placebo).

In both treatment arms, remifentanil affected both ventilatory frequency and tidal volume (Supplementary Fig. S2). In the remifentanil/esketamine and remifentanil/placebo arms, remifentanil reduced ventilatory frequency from 17.1 (3.7) to 14.7 (3.1) bpm ($P<0.01$) and 17.5 (2.9) to 14.9 (2.5) bpm ($P<0.01$), respectively, and tidal volume from 1220 (283) to 853 (955) ml ($P<0.01$) and 1150 (222) to 812 (113) ml ($P<0.01$), respectively. Esketamine had a selective effect on ventilatory frequency with an increase from 14.7 (3.1) to 18.6 (3.9) ($P<0.01$). Tidal volume showed a small albeit insignificant increase 853 (156) to 955 (396) ml by esketamine. Placebo had no effect on either ventilatory frequency or tidal volume.

PK–PD analysis

The PK parameter estimates are given in Supplementary Table S1. The parameter estimates of the final three-compartment model were similar to that of Sigtermans and colleagues,[19] with the exception of the clearances that were 83 (2)% of the earlier estimates. Goodness of fit plots are given in Figure 2A–C, showing measured *vs* individually predicted esketamine concentrations (Fig. 2A), conditional weighted residuals with $\eta-\varepsilon$ interaction (CWRESI) *vs* time (Fig. 2B) and the NPD (Fig. 2C). All indicate that the model adequately described the data.

The best PD model (Table 1 and Supplementary Table S2) is a mixture model with remifentanil effect on Y1 and Y2, an esketamine effect on C_D^K2 (i.e. Y2) and Q fixed to 1. The PD parameter estimates of the best model are given in Table 1. Examples of data fits are given in Figure 3 for an esketamine responder (Fig. 3A, median fit with $R^2=0.719$), an esketamine non-responder (Fig. 3b), a placebo responder (Fig. 3C) and a placebo non-responder (Fig. 3D, best fit with $R^2=0.952$). Goodness of fit plots are given in Fig. 3D–F. Inspection of the individual fits and the goodness of fit plots indicate that the model adequately described the data.

Remifentanil effect

The model has two ventilation components [Y1 and Y2, equations (2) and (3)] at which remifentanil acted. The effect of remifentanil was 39% at Y2 and 61% at Y1 [compare parameter λ of equation (4) and Table 1]. Remifentanil acted on the two ventilation components with different potencies and dynamics. Y1 is affected more slowly [$t_{½R1}$=12.2 (2.6) min] with relatively low potency [$C_{50}1$=1.24 (0.15) ng ml^{-1}] and high G1 [8.44 (0.64)] than the remifentanil effect at Y2 [$t_{½R2}$=2.15 (0.49) min, $C_{50}2$=0.46 (0.06) ng ml^{-1} and G2=4.44 (0.64)]. The existence of the two components is well illustrated in Fig. 3D, a

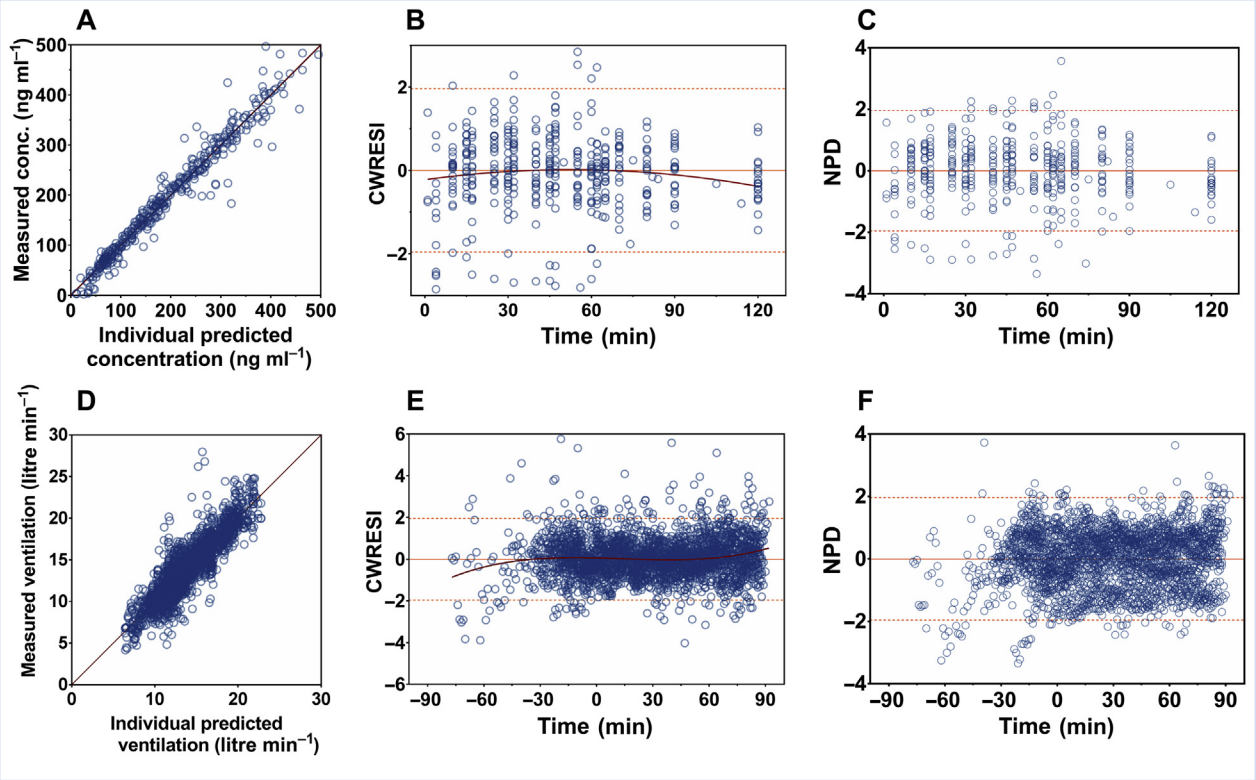

Fig 2. Goodness of fit plots of the pharmacokinetic (A–C) and the pharmacodynamic models (D–F). Panels (A,D) are the measured *vs* the individual predicted esketamine concentration and ventilation, respectively; (B,E) are the conditional weighted residuals with η–ε interaction (CWRESI) *vs* time for esketamine concentration and ventilation, respectively; and (C,F) the normalised prediction discrepancy for esketamine concentration and ventilation, respectively. In (B,E) the red line is a smoothing curve; in (B,C,E,F) the orange lines are the median (solid line) with 95% confidence intervals (CI) (broken lines). NPD, normalised prediction discrepancies.

Table 1 Pharmacodynamic parameter estimates. $\dot{V}_{BLN}$is baseline ventilation, $C_{50}1$ is the remifentanil concentration causing a 50% decline of V_{BLN}, $C_{50}2$ is the remifentanil concentration causing a 50% decline the ventilatory CO_2 sensitivity, $t_{½R1}$ and $t_{½R2}$ are the blood-effect-site equilibration half-times linked to components Y1 and Y2, respectively [equations (1) and (2)], G1 and G2 are shape factors of components Y1 and Y2, respectively [equations (1) and (2)], λ is a constant, C_D^K1 and C_D^K2 are the esketamine concentration causing a doubling of remifentanil potency parameters $C_{50}1$ and $C_{50}2$, respectively, Q a shape parameter [equations (3) and (4)], P the responder rate and σ^2a the additive residual error. SEE, standard error of estimate

	Estimate	SEE	ω^2	SEE	ν^2	SEE
Remifentanil effect on ventilation						
$\dot{V}_{BLN}$ (litre min^{-1})	20.1	0.26	–	–	0.006	0.002
λ	0.39	0.01	–	–		
$C_{50}1$ (ng ml^{-1})	1.24	0.15	0.14	0.07		
$C_{50}2$ (ng ml^{-1})	0.46	0.06	0.14	0.08		
$t_{½R1}$ (min)	12.2	2.6	0.26	0.12		
$t_{½R2}$ (min)	2.15	0.49	0.49	0.37		
G1	8.44	0.64	0.24	0.08		
G2	4.37	0.64	0.24	0.08		
Esketamine effect on remifentanil-induced respiratory depression						
C_D^K1(ng ml^{-1})	–	–	–	–		
C_D^K2 (ng ml^{-1})	127	33.9	0.37	0.17		
Q	1 (FIX)	–	0.72	0.36		
$P_{(Responder\ to\ esketamine)}$	0.83	0.12				
$P_{(Responder\ to\ placebo)}$	0.23	0.15				
σ^2a	2.39	0.54				

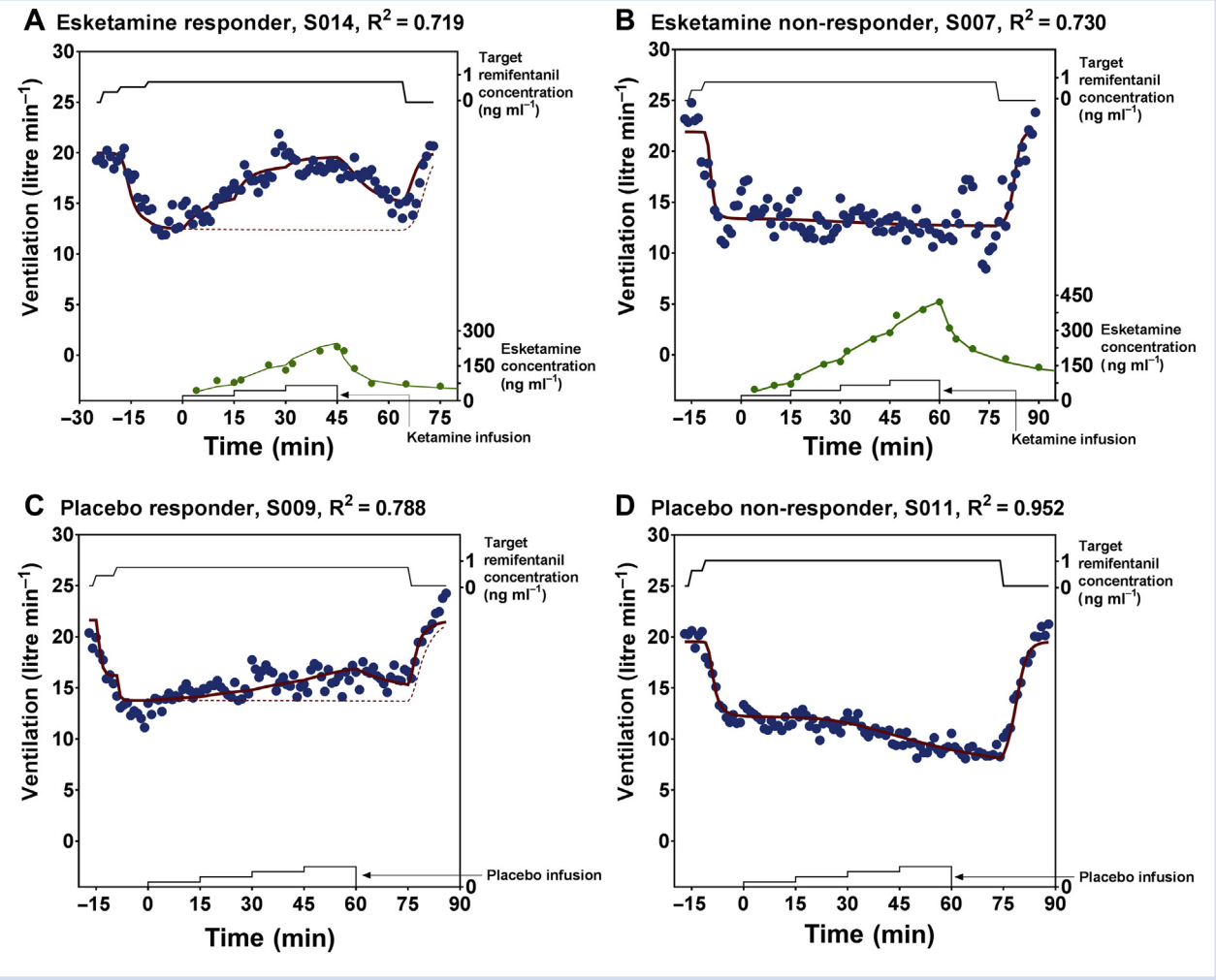

Fig 3. Pharmacokinetic and pharmacodynamic data fits of an esketamine responder (A; median fit), an esketamine non-responder (B), a placebo responder (C) and a placebo non-responder (D; best fit). The data show the esketamine concentration (green dots), pharmacokinetic data fits (green lines), the measured ventilation (blue dots), the pharmacodynamic data fits (continuous red lines), the effect of remifentanil *without* the presence of ketamine or placebo (A,C, red broken lines), ketamine or placebo infusion schemes [green surfaces in (A,B), yellow surfaces in (C,D)] and the target remifentanil concentration (black lines).

placebo experiment, where an initial rapid decrease in ventilation is followed by a slow further decline. The absence of an Y1 component in some subjects is explained by the fact that the slow component was only present when target remifentanil concentrations were relatively high and occurred with a steep concentration–response relationship. This reflected by the relatively high values of parameter estimates $C_{50}1$ and G1.

Esketamine and placebo effects

Esketamine had an exclusive effect on component Y2 and doubled $C_{50}2$ at a concentration of 127 (34) ng ml^{-1} (C_D^K2); an effect on $C_{50}1$ was not identifiable. Esketamine blood-effect-site equilibration half-time ($t^{1}/_{2}{}_E$) was not significantly different from 0, indicative that the esketamine effect was driven by plasma PK. In some subjects, a response to placebo treatment was observed (see Fig. 3C for an example). To quantify the placebo effect, it was assumed that esketamine was present and had an effect of $C_{50}2$. This led to a placebo potency parameter C_D^K2(placebo) with value 363 (37.5) ng ml^{-1}, a factor of 3 smaller than the esketamine C_D^K2. Probability of being a responder to esketamine or placebo was 83 (12)% and 23 (15)%, respectively, which corresponds to 10 responders to esketamine and three to placebo.

Dose–response relationship

To get an indication of the steady-state dose–response relationships, the two inputs to the PD model are plotted against ventilation in Figure 4. Figure 4A gives the target remifentanil concentration–ventilation relationship at several esketamine concentrations (ranging from 0 to 400 ng ml^{-1}); Figure 4B gives the esketamine concentration–ventilation relationship at a number of target remifentanil concentrations (ranging from 0 to 2 ng ml^{-1}). In both Figure 4A and B, the maximum observed concentrations are depicted by the grey broken lines. All values beyond these lines are extrapolations. Figure 4C combines the data from Figure 4A and B and gives the

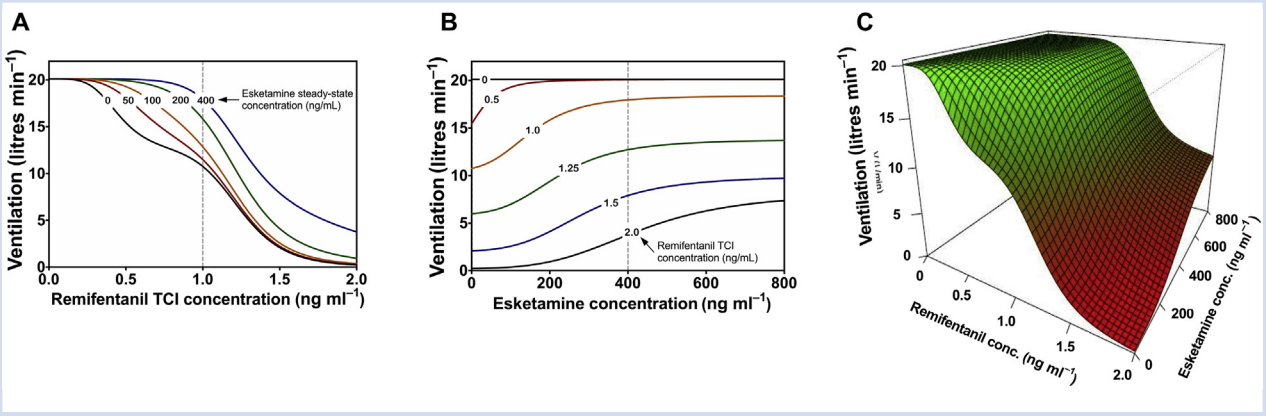

Fig 4. (A) Steady-state relationship of target remifentanil concentration *vs* ventilation at increasing esketamine steady-state concentrations (0–400 ng ml^{-1}). The grey broken line reflects the mean target remifentanil concentration applied in the study. The effect of target remifentanil concentrations > 1 ng ml^{-1} on ventilation are extrapolations. (B) Steady-state relationship of esketamine concentration *vs* ventilation at increasing target remifentanil concentrations (0–2 ng ml^{-1}). The grey broken line reflects the peak esketamine concentration observed in the study. The effect of esketamine concentrations > 400 ng ml^{-1} on ventilation are extrapolations. (C) Response surface of the interactive effect of steady-state esketamine concentration (*y*-axis), target remifentanil concentration (*x*-axis) *vs* ventilation (*z*-axis).

response surface of esketamine concentration (*y*-axis), target remifentanil concentration (*x*-axis) against ventilation (*z*-axis).

Effect of esketamine on poikilocapnic ventilation

Esketamine plasma concentrations of the observational study were similar to those observed in the randomised trial (Fig. 1A), with peak plasma concentrations of 378 (24) ng ml^{-1}. Esketamine induced a small decrease in end-tidal PCO_2 of 0.4 kPa from 5.2 (0.3) kPa (baseline) to 4.8 (0.4) kPa (last minute of esketamine infusion; paired *t*-test: $P<0.01$) but had no effect on ventilation [$\dot{V}_{BLN}$changed from 8.9 (0.6) litre min^{-1} (baseline) to 9.4 (1.6) litre min^{-1} (last minute of esketamine infusion), $P=0.12$]. Changes in ventilation and end-tidal PCO_2 were restricted to the final minute of the highest esketamine infusion (Fig. 1D).

Discussion

The main findings from our study are that esketamine dose-dependently reverses remifentanil-induced respiratory depression, while it has a little or no effect when ventilation is not depressed by the opioid.

PD model

Remifentanil effect

We constructed a PD model in which both remifentanil and esketamine could affect breathing *via* actions at component Y1, component Y2 [equations (2–4)], or both. We observed that remifentanil reduced ventilation via an effect at both parts, at Y1 with relatively low potency and slow dynamics, and at Y2 with relatively high potency and faster dynamics (Table 1). The initial rapid decrease in ventilation after the start of remifentanil infusion is a result of its effect on Y2, while the slow decrease in ventilation that was observed in some subjects was a result of an effect at Y1. In mammals, ventilatory control has CO_2-sensitive and CO_2-insensitive components as described in equation (1), where $\dot{V}_{BLN}$ is the CO_2-insensitive and S the CO_2-sensitive component.[18,23,24] In our analysis, we link a drug effect at Y1 to an action at CO_2-insensitive ventilation, while an effect at Y2 is linked to the CO_2-sensitive operator of ventilation. These associations seem hypothetical but are plausible when we take the results of visit 3 into account where esketamine had little effect on resting ventilation (i.e. Y1 or $\dot{V}_{BLN}$); see also the following section (*Esketamine effect*).

We did not directly estimate the value of S in our analysis. However, parameter λ is an indirect estimate of S. Since $\lambda \times Y2 = S \times (P_TCO_2 - P_{TB}CO_2) \approx 8$ litre min^{-1}, the value of S is estimated to be approximately 8 litre min^{-1} kPa^{-1} (assuming that $P_TCO_2 - P_{TB}CO_2 \approx 1$ kPa),[24] which is within the range of ventilatory CO_2 sensitivities observed in healthy young volunteers.[24] The reason for a difference in remifentanil potency and dynamics at components Y1 and Y2 remains unknown but could be related to the opioid effect on central neuronal dynamics, causing a slow reduction of CO_2-insensitive ventilation.[25]

Previously we tested the effect of remifentanil on ventilation in open loop conditions.[26] The remifentanil effect in that study was modelled with just one component with values for C_{50} (1.6 ng ml^{-1}) and $t_{½R}$ (0.53 min) in the same range as in the current study for Y2. We relate the inability to detect a slow component (Y1) to the short infusion times (0.5–6 min) and open loop (i.e. poikilocapnic) conditions in that study. With respect to the latter condition, any slow reduction in ventilation might have been counteracted by the slow increase in arterial CO_2. Apparently, the open-loop PD model was unable to detect such a slow effect, if at all it occurred in these short infusion experiments.

Esketamine effect

Esketamine (at a cumulative dose of 40 mg) exclusively impacted on Y2. We argue that (low-dose) esketamine interacts with the ventilatory control system under conditions that the central respiratory network is affected by an opioid (i.e. under conditions of hypoventilation). We come to this conclusion as the same esketamine dose had only a limited effect under

baseline conditions (i.e. without the presence of an opioid; visit 3). Consequently, as remifentanil and other opioids reduce ventilatory CO_2 sensitivity,[20,27–29] our data suggest that esketamine increased CO_2 chemosensitivity (i.e. parameter S) after its reduction by remifentanil. Also, other respiratory stimulants acting within the respiratory network, such as the ampakines, stimulate breathing exclusively under conditions of hypoventilation by increasing the (reduced) ventilatory CO_2 sensitivity.[29,30] Still, we cannot exclude some albeit small esketamine effect at $\dot{V}_{BLN}$ as the data from visit 3 still indicate some effect on ventilation, which might have been underestimated a result of the open loop conditions of visit 3.

Esketamine- and racemic ketamine-induced stimulation *vs* depression of breathing

While some experimental work in both animals and humans shows racemic ketamine-induced respiratory stimulation in agreement with our observations,[12–15] others show an inhibitory effect of ketamine on ventilation.[31–35] For example, Bourke and colleagues[31] studied the interaction of racemic ketamine and morphine in six male volunteers. Using an experimental design very similar to this study, they showed a dose-dependent reduction of isohypercapnic (end-tidal PCO_2 6.6 kPa) ventilation by ketamine (cumulative dose increased from 0.39 to 3.0 mg kg^{-1}) and morphine (0.2 and 0.4 mg kg^{-1}); the combination of ketamine and morphine had an additive negative effect on breathing.[31] Using CO_2-rebreathing, Hamza and colleagues[35] showed a 40% reduction of the slope of the $\dot{V}_E - CO2$ response by an anaesthetic dose of racemic ketamine (2 mg kg^{-1} followed by 0.04 mg kg^{-1} min^{-1}) in a paediatric population (age 6–10 yr). We previously observed in mice that esketamine produced a dose-dependent reduction of the $\dot{V}_E - CO2$ response slope in a dose range of 10–200 mg kg^{-1}, with frequent inspiratory pauses in the higher dose range.[32] Differences in species, dose, ketamine formulation or experimental set-up can only explain part of the differences in study outcomes. For example, our cumulative esketamine dose of 0.57 mg kg^{-1} esketamine falls well within the dose range studied by Bourke and colleagues,[31] even when taking into account a possible potency difference between racemic ketamine and the S(+)-isomer.[36] Possibly, ketamine's metabolites are involved in the respiratory effects of the parent drug (see item (iii) in paragraph "Mechanism of esketamine-induced respiratory depression"). If so, then differences in PK among species and between isomers may explain some of the observed differences. It is important to realise that we and others observed a ketamine-induced stimulatory effects on breathing at subanaesthetic ketamine doses.[13,15] In rats, Eikermann and colleagues[14] showed that respiratory stimulation persists even at anaesthetic doses, while Hamza and colleagues[35] found the reverse in children. Further human studies are needed to fully understand the complex behaviour of the low- and high-dose ketamine isomers on breathing.

An interesting observation is that, in contrast to remifentanil, which reduced both tidal volume and ventilatory frequency, esketamine selectively increased ventilatory frequency (Supplementary Fig. S2). It has recently been proposed that tidal volume is regulated by metabolic stimuli, while respiratory frequency is driven by fast non-metabolic factors.[37,38] Our findings then suggest that remifentanil has a metabolic effect, while the esketamine effect was related to non-metabolic stimuli (e.g. stress, behavioural stimuli, or both). This seems to disagree with the findings of this study that esketamine increased ventilatory CO_2 sensitivity, which is a component of metabolic control.[38] Additionally, the proposed mechanisms of esketamine-induced respiratory stimulation all seem metabolic in nature (see below). Possibly, behavioural effects of isohypercapnia may have affected the study outcome. However, all subjects who completed the study were highly comfortable during all three visits. Further studies are needed to address the mechanistic pathway of esketamine within the ventilatory control system.

Extrapolation of our results to higher remifentanil concentrations suggests that even in case of the complete cessation of breathing (i.e. opioid-induced apnoea), low-dose ketamine may restore breathing activity (Fig. 4). Further studies are needed to verify the validity of our model at deep levels of respiratory depression (e.g. at remifentanil plasma concentrations >1.25 ng ml^{-1}). If corroborated, ketamine behaves similarly to CX717, an ampakine that restores respiratory activity following fentanyl-induced apnea.[10] However, ketamine does not appear to act like drugs that exert their effect at the carotid bodies or drugs with reduced efficacy at deeper levels of opioid-induced respiratory depression (*i.e.* ceiling behavior).[39]

Mechanism of esketamine-induced respiratory stimulation

Although our study was not specifically designed to unearth the mechanism of the stimulatory effect of esketamine on breathing, it is relevant to discuss possible mechanisms. (i) Esketamine produces a strong increase in sympathetic outflow and reduces the reuptake of neuronal norepinephrine.[19] Monoaminergic neurotransmitters play an important role in ventilatory control.[40] Increased synaptic concentrations of noradrenaline stimulate breathing activity and increase ventilatory CO_2 reactivity.[41,42] (ii) Esketamine may stimulate breathing though *N*-methyl-D-aspartate receptor blockade. Some indirect evidence comes from an animal model of the Rett syndrome.[43] Patients with Rett syndrome have mental retardation and experience severe breathing irregularities because to mutations in the *MECP2* gene. In a mouse model of Rett syndrome, ketamine reduced the number of apnoeic events by actively stimulation of breathing activity. (iii) Finally, it may well be that the esketamine metabolite hydroxynorketamine contributed to the respiratory effects of the parent drug. Hydroxynorketamine is an agonist at the AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) receptor.[44] AMPA receptors are expressed in the brainstem respiratory network, for example within the pre-Bötzinger complex, an area of the brain involved in respiratory rhythmogenesis, and play an important role in the maintenance of respiratory drive.[45,46] Of interest is the observation that so called ampakines, drugs that act selectively at the AMPA receptors, increase the respiratory drive in both animal and human studies, but, as stated earlier, only under conditions of hypoventilation.[29,30] For example, the ampakine CX717 counters alfentanil-induced respiratory depression to a 50% depression of $\dot{V}_E - CO2$ sensitivity.[29] An effect of esketamine via hydroxynorketamine at AMPA receptors may explain the absence of response in some subjects who are poor metabolisers. This remains speculative at present, as we did not measure hydroxynorketamine plasma concentrations in our subjects. Future studies will need to resolve whether hydroxynorketamine plays an important role in the respiratory effects of ketamine. If so, this would mirror the

observation in rodents that hydroxynorketamine rather than ketamine plays a major role in the generation of its antidepressant effects.[44]

In summary, we observed that remifentanil depressed ventilation in healthy volunteers by reducing ventilatory CO_2 sensitivity, an effect that was partially countered by esketamine. These findings could indicate that the use of low-dose esketamine in postoperative patients may not only reduce opioid consumption but will also stabilise breathing and consequently reduce the probability of fatal events. The esketamine dose needed for such an effect is between 12 and 24 mg h^{-1} (for a 70 kg patient). However, the observed advantageous effects of esketamine should be balanced against its side effect profile, most importantly the psychedelic symptoms that may be perceived by some patients as extremely frightful. We believe that additional studies are still needed and we plan to construct esketamine utility functions to determine the optimal esketamine dose that produces respiratory stimulation with minimal side effects.[47,48]

Authors' contributions

Involved in the inception of the project: M.N., L.A., E.S.
Performed the experiments and aided in the data analysis: K.J., E.R., A.D.
Performed the PK–PD modelling: E.O.
Wrote part of the protocol: M.V., M.N., A.D.
Principle investigator of the project: M.N.
Supervised the project: M.V.
Supervised the experiments: M.N.
Wrote part of the paper and its revision, and approved the final version of the manuscript: all authors.

Declaration of interest

A.D. is chairman of the Institutional Review Board of Leiden University but was not involved in the review of this study.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.bja.2018.02.021.

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